TREATMENT in General Practice

HARRY BECKMAN, M.D.
Professor of Pharmacology, Marquette University
School of Medicine, Milwaukee, Wisconsin

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MADE IN U S A

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W B SAUNDERS COMPANY
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To my wife

JANE SMITH BECKMAN

and our sons

THOMAS HOWELL BECKMAN

and

JOHN ROSS BECKMAN

PREFACE

The neglect of thorough and painstaking teaching of therapeutics in this country is not so often the subject of serious consideration in our medical councils as it well might be. With only a few notable exceptions, the medical schools seem content if there is presented within their halls, usually to Junior students who have had as yet practically no contact with the sick, a ridiculously inadequate course of lectures, the rest being left to the teachers in the departments of medicine, pediatrics, obstetrics, etc. And these latter seem to shift the responsibility largely onto the gods, not through any culpability upon their part, but simply because in their immersion in the task of acquainting the student with the prodigious methodology of modern diagnosis no time is left for an exhaustive consideration with him of the treatment of disease. Hence it is that the therapeutic credo of the average young practitioner today contains but two articles: one, that there are certain therapeutic principles that invariably hold and that they need to be varied only in detail in the handling of particular diseases, and, the other, that the art of treatment is one that "comes" if only one has mastered the art of diagnosis.

It is in an attempt to shake, however feebly, the false foundations of these beliefs that the present book has been written. In it each of the principal diseases of man, exclusive of those that by prescriptive right belong within the domain of the legitimate specialties, has had its own peculiar therapy described, as that therapy has been evolved out of the experience of physicians all over the world. The true authors of the book, then, are those men and women whose names appear in the Bibliography. Whenever possible I have presented their work in their own words, but often it has been necessary to abstract and to condense, and not infrequently to present a subject in a manner and perhaps even from a point of view that has apparently little in common with that held by those who reported the original trials and observations. Always, however, I have looked upon myself merely as an editor, and I hope that no more than editorial liberties have been taken in any portion of the book. Of course it has not been possible to keep my own opinion invariably in the background, hence I elected in the beginning to write in the first person so that there might be at no time any confusion as to whose work or views were being presented.

indolent type of pedagogy that seeks sanctuary in the shameful words: "Upon this point we can say very little as the authorities are at present in disagreement." Only as I have thought and taught through the years have I been able to write, a limitation which I suppose every author recognizes. As for the many other shortcomings of the book, I can only assure the reader that, no matter how grievous he finds them, they can in no wise affect him so deeply as they do me, for only I can know with what bright hopes the work was planned and begun several years ago.

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ACUTE INFECTIOUS LYMPHOCYTOSIS

In 1941, Smith reported two types of lymphocytic reaction of the blood that he designated as acute and chronic infectious lymphocytosis. The acute cases, which were the less frequently seen, manifested a short but striking leukocytosis with only minimal symptoms and physical signs of a nondi-

and Beloff and Gang (1945) recorded a case in which the clinical picture resembled that of poliomyelitis. As the result of more extensive experience, Smith (1944) enlarged upon his description of the acute form of the disease and stated that hyperleukocytosis, with a relative and absolute lymphocytosis due to an increase in normal small lymphocytes, constitutes the most important element in the diagnosis. Elevated blood levels are said to persist from three to nine weeks, the normal lymphocytes in this disease contrasting

here. Biopsy of the lymph nodes in two of Smith's cases revealed degeneration of the lymph follicles and striking proliferation of the reticuloendothelium of the sinuses. Smith's report of three patients from one family and one hospital contact, together with Finucane and Philips' (1944) report of an epidemic of twenty cases in a children's ward, indicates that the disease is both infectious and contagious; the possible incubation period seems to be between twelve and forty days. All of the reported cases have been in children save for three cases in young adults, two seen by Duncan (1945) and one by Yuskis (1946)

THERAPY

There is nothing to describe.

AINHUM

Ainhum is a disease that attacks the toes, usually but one toe at a time. A furrow appears at the digitoplantar fold and slowly extends and encircles the toe until it is separated from the foot. There is usually no pain, but the patient is often greatly inconvenienced by the fact that the toe beyond the constriction becomes bulbous and in the late stages dangles in an everted position The course of the disease is slow, self-amputation usually occurring

nly after a number of years. Ainhum occurs in the dark-skinned races in ndia, Africa, Central and South America and the West Indies, and a few ndigenous cases in Negroes have been seen in both Europe and the United States.

Kean and Tucker (1946), who reviewed the literature, studied their own dozen cases, and reviewed the records of forty-five persons suffering from ainhum on the Isthmus of Panama, concluded that the pathogenesis of this disease is still not clear and that its cause remains unknown. However, Shaffer (1947) reported a case in a white patient with diabetes mellitus, indicating that ainhum may be a symptom and not truly a disease entity.

THERAPY

At present the only effective treatment consists in amputation of the involved toe.

AMEBIASIS

(Amebic Type of Dysentery)

Amebiasis is an infectious disease caused by *Endamoeba histolytica.* The organism causes more or less extensive areas of ulceration throughout the large bowel, giving rise to the symptom-complex of amebic dysentery; entering the blood stream it is also sometimes carried to the liver, where it may cause serious abscess By extension, lung involvement sometimes occurs, and indeed pulmonary amebiasis without a "primary" liver abscess and liver abscess without antecedent dysentery are not unknown; I have seen reports of the involvement of the following other organs: uterus, lung, pleura, brain, kidney, ovary, bone, pericardium and vagina Ulcers of the skin may occur after surgical drainage of an amebic abscess or in the anal and penile regions by direct extension from the rectum Klatskin (1946) found amebiasis a common cause of urticaria and angioneurotic edema in India, and Witherspoon (1946) reported a case in which there was very suggestive association of exfoliative dermatitis with amebic dysentery. Granulomas of the lower bowel, resembling carcinoma in many respects, have been reported a number of times. In a very critical review, Watson (1945) developed the reasons why urinary amebiasis is extremely rare.

Amebiasis is acquired by ingestion of the encysted form of the organism which has been passed from the bowel not of an acutely ill patient but one who is convalescent or is a chronic carrier of the cysts, thus it may be propagated by fecal pollution of garden truck or of food during its handling or its exposure to flies, or by the drinking of feces-polluted water, or by direct contact between individuals as seems sometimes to be the case in prison and asylum epidemics. It usually begins gradually, after an incubation period of roughly seven to seventy-seven days (Chicago epidemic of 1933), with intermittent attacks of bloody, mucoid diarrhea, without nausea, loss of appetite or fever, and with only moderate tenesmus and abdominal pain; occasionally however, the attack is fulminating and of the acute appendicitis type, an in "chronic appendicitis" this disease should be thought of also In som instances secondary bacterial invasion of the bowel occurs, the patie becomes anemic and emaciated, and in a few years is exhausted out of l

but an outstanding characteristic of the disease in the vast majority of cases is its chronic and intermittent course. The laboratory diagnosis of amebiasis requires special knowledge and skill; the roentgen appearance of the colon will not alone establish the diagnosis A complement-fixation test is in process of development but is still looked upon, according to Kent and Rein (1946), of the Army Medical School, as of adjunctive rather than of primary value in diagnosis.

Since amebiasis is well known to exist in tropical and subtropical countries it has been commonly thought to occur only in these regions, but many studies

these epidemics do not show seasonal preference. Infants and children as well as adults may be affected. Craig's "very conservative" estimate is that between 5 and 10 per cent of the people in the United States are infected with *E histolytica;* Faust (1942) felt that possibly 20 per cent would be a more nearly accurate figure, but Hood (1943) found an incidence of only 7.9 per cent in the 2,000 patients and employees of a hospital in Chicago, the study extending over a twelve-year period which included the epidemic years in that city. Birnkrant *et al.* (1945) found that 13.9 per cent of the food-handling inmates of a large hospital for the insane in New York City were ameba carriers Michael's (1946) survey of 1,000 patients recently returned from War II duty in the Pacific Ocean area revealed 8.9 per cent infection with *E. histolytica;* Marion and Sweetsir's (1946) report on 1000 military returnees from the European area revealed an incidence of 16.8 per cent.

THERAPY

Prewar Methods.—The world entered War II with the belief, soundly based upon experience, that the treatment of intestinal infection with *E. histolytica* was a relatively simple matter with a successful outcome practically assured. One simply gave two of the "specific" drugs in combination for a while, using some emetine also in the beginning if the case was acute, then after a suitable interval repeated this course a time or two and expected in nearly all instances to have a cured patient. Experience in War II, however, challenged this viewpoint for there arrived a large number of cases from the India-Burma theater that did not respond to this treatment at all It therefore became necessary to submit the therapy of amebiasis to a most critical review.

Lessons of War II.—While most British and American workers are not in agreement with Brumpt who believes that there are certain particularly pathogenic strains of amebae, nevertheless this question arose again, but I believe it was satisfactorily settled by the study of Karl and Sloan (1946),

Adams (1945), Priest (1945), Manson-Bahr (1945), and Hargreaves (1946) crystallized the causes for the failure in the treatment of amebiasis in that disastrous Burmese campaign about as follows: (a) There was failure to realize that emetine alone will only rarely eradicate an amebic dysenteric infection,

yet in many of these cases it had been used to the exclusion of other drugs and its use persisted in long after it was apparent that it was not going to sterilize the patient. Further, the emetine was injected almost exclusively, which is a bad practice for the reason that such emetine is not excreted into the gut and does not reach the precystic forms there. Other forms of emetine should have been given concomitantly by mouth but this was almost never done. This practice of administering emetine parenterally alone and for too long a period very probably rendered the organisms emetine-fast so that when the drug was subsequently administered it was no longer effective whether given by injection or by mouth. (b) It is possible that an infection made emetine-fast then yields much less readily to the other drugs which, even under the most ideal circumstances, are often not sufficiently absorbed to destroy the parasites that have invaded the tissues. (c) The conditions obtaining in the war zone in which these cases were primarily treated often did not permit of that care for the minutiae of detail in therapy which is so important in the treatment of amebiasis. (d) The patients were often exhausted, debilitated and ill-nourished war casualties who required in addition to drugs just that sort of building-up treatment which was impossible in the war zone and oftentimes in many hospitals to which they were evacuated far from that zone. (e) Many of the bacteria normally present in the feces being able to gain access into the bowel wall through the ulcerated mucosa, undoubtedly many of these patients had serious infections of a secondary nature. (f) Much is still to be desired of chemotherapy in this field since none of our drugs in any of their combinations is as yet ideal, but no such failures as were experienced in this campaign should occur if the regimen of therapy is well devised with the drugs available today and the conditions for its meticulous execution obtain.

Incorporation of Penicillin and Sulfonamides Into the Scheme.—Hargreaves (1945), at the suggestion of General Biggam, as a last resort tried penicillin in an apparently moribund patient. The result was dramatic and brought about the incorporation of this new agent into the treatment of distressing cases; it has not been found to have any significant effect on *E. histolytica* but it does bring about striking symptomatic relief and seems to render severe refractory cases of chronic amebic dysentery more amenable to the specific drugs. Sulfasuxidine has also been added to the scheme to combat some of the organisms which are not sensitive to penicillin.

U. S. Army Plan of Treatment.—I shall set down here in abbreviated form the plan employed by the Army Medical Department toward the close of War II, for it employs all of the principles discussed above and has been used with great satisfaction.

Course A (for acute cases with vegetative E. histolytica in the stools).—Emetine hydrochloride daily by hypodermic injection for four to six days will usually control the acute symptoms, but it should nevertheless be followed at once without any interval by the oral administration of emetine-bismuth-iodide for twelve consecutive days. Along with the emetine-bismuth-iodide there should be given daily a retention enema of chiniofon (yatren). During the succeeding twelve days the patient should be given diodoquin, or as second choice carbarsone or acetarsone (stovarsol), by mouth and may be allowed to get up and begin his convalescence. Since in particularly acute attacks it has often been found that bacillary dysentery is present as a complication, it is of benefit to give sulfasuxidine along with the emetine injections.

Course B (for patients who are passing cysts but not vegetative forms of E.

histolytica and who present neither acute dysentery symptoms nor indications of hepatitis).—Omit the emetine injections but otherwise treat precisely as in *Course A.*

Course C (for intractable cases that resist ordinary treatment).—Cases that resist *Course A* will usually respond to it after a preliminary course of penicillin and sulfasuxidine has eliminated secondary pyogenic organisms which have become established in the diseased bowel wall.

When cure is not obtained by following any of the above courses it is well to allow a rest interval of ten to twelve days and then repeat the whole course.

Criteria of Cure.—Because of the notorious liability of amebiasis to relapse, stools should be examined macroscopically at regular intervals during treatment and microscopically on six consecutive days at least two weeks after all treatment has been completed, sigmoidoscopic examination for a test of cure should also be performed after this interval.

Treatment of Complications.—Abscesses of the lung and of the brain require the usual treatment for these conditions plus the systemic use of emetine, the response is practically always excellent since the vegetative forms, which alone enter the tissues, are more susceptible to the action of the drug than are the [illegible]

is much preferable to surgical drainage when there is no secondary infection; unless the symptoms *demand* immediate aspiration it is often well to give the emetine full chance, for if this is done the puncture can be avoided not infrequently. Berne (1942) treated sixty-three cases as follows. nineteen patients, including three who had hepaticobronchial fistula, were treated with emetine alone and all recovered, eighteen patients were treated with emetine and subsequently aspirated and all recovered; twenty-six patients were treated by open surgical drainage, some with and some without emetine, and fourteen of them died. Klatskin (1946) successfully treated sixty-eight of sixty-nine patients with emetine without either aspiration or surgical drainage. Ochsner and DeBakey (1943) reported a mortality of 3.6 per cent in eighty-three cases in which emetine with or without aspiration was employed and a mortality of 22 1 per cent when open drainage was performed. Walters *et al.* (1944) stated the opinion that open surgical drainage should be employed only when acute perforation into the peritoneum or pleura is actual or impending or when there is proved pyogenic contamination In a case of hepatic abscess in which [illegible]

into the cavity; the patient was given a total of 830,000 units during a period of fifteen and one-half days, injection being made at four-hour intervals [illegible]

[illegible]

of amebae from the pus.

The specific amebacidal agents other than emetine, all being at least

potentially hepatotoxic, should not be employed in cases of known liver abscess until emetine, with or without aspiration, has brought about subsidence of the liver involvement.

Parenteral Emetine.—The dose of emetine hydrochloride for injections is one-half grain (30 mg.) twice daily or 1 grain (60 mg.) once daily for four to six days, only in exceptional instances, as in some cases of recalcitrant hepatic amebiasis, is the series of injections extended to perhaps as much as twelve days. Dosage for children is scaled in accordance with their weight but the drug is usually not given to infants at all. Subcutaneous injection is not infrequently followed by pain and discoloration of the skin and very rarely

syringe one can be sure of not being in a vein; even so, absorption is undoubtedly faster by this route which probably causes many men to hesitate to employ it. It has been said that the injections may be rendered painless by using a 1 to 2 per cent procaine hydrochloride solution as solvent for the drug; it would seem that toxic effects need not be feared from such a practice except in individuals hypersensitive to procaine. Emetine is said to cause very great pain when introduced in enema form, intravenous administration is regarded almost universally as unnecessarily dangerous, though Heilig and Visveswar (1943), in India, did not hesitate to introduce the drug by this route in a rather large series of cases.

Oral Emetine.—In a preliminary study employing a small group of patients at Gorgas Hospital in the Canal Zone, Shrapnel *et al.* (1946) used one-third grain (20 mg.) enteric-coated tablets of emetine hydrochloride by mouth, giving one tablet three times daily for twelve days to seven patients and two tablets three times daily for six days to six patients. No serious toxic reactions were noted and vomiting, without either nausea or cramps, occurred very infrequently. Since the results of treatment seemed to be satisfactory, considering the fact that no other drugs were used in combination with the emetine, it is to be hoped that a more extensive trial of this method will soon be reported.

Emetine-Bismuth-Iodide.—This agent is given by mouth in doses of three grains (0 2 gm.) daily for usually twelve consecutive days The dose is best given at night in a gelatin capsule and may be accompanied by a barbiturate to allay the nausea; the stools must be watched for a dark brown or black color denoting that the capsules have disintegrated properly.

Emetine Toxicity.—Before emetine therapy was standardized at the lower dosage nowadays employed we knew that the drug frequently caused an increase in diarrhea often accompanied by nausea, also there were sometimes caused rapidity, irregularity and weakness of the heart beat, changes in the skin and nails, asthenia, neuritis (myositis) and palsy; Manson-Bahr (1941) cited a case in which progressive wasting and eventually a state resembling progressive muscular atrophy was thought to have been due to the use of the drug. Some deaths, apparently in auricular fibrillation, have been reported. Some of these cases were undoubtedly instances of idiosyncrasy to the drug and many others were due to the use of greatly excessive dosage. Brown (1935), reviewing the 554 cases of the Mayo Clinic in which emetine had been used within the limits of our present dosage scheme, found only three reactions in the series. Nevertheless, Hardgrove and Smith (1943), in Panama, observed

electrocardiographic changes in thirty-eight of seventy-two patients r emetine; comparable findings were reported by Cottrell and Hayward and in the series of Heilig and Visveswar (1943) in India, nine of the patients with initial normal cardiograms showed some deterioration; stra enough, in this latter series improvement was shown by a high percenta patients with previously pathological tracings. It would certainly seem considering the high usefulness of the drug, its employment is not unc dangerous if one keeps the patient in bed, is watchful, and bears it in m that the chances of myocardial injury probably increase beyond the age sixty. Pregnancy, as well as cardiovascular disease, are considered to contr indicate the use of emetine.

Emetine Resistance.—As earlier stated in this article, part of the failure to control amebiasis during and since War II have been laid at the door of emetine "fastness," but it is only fair to state that Hargreaves (1945), a very competent observer in this field, feels that there is as yet no scientific evidence that emetine-resistant strains of *E. histolytica* exist or can be produced The reader is referred to Hargreaves' paper for a review of the subject

Chiniofon (Yatren) Enemas.—Enemas of chiniofon, at first 200 cc. of a 2.5 per cent solution but building up in quantity and strength if well tolerated, are usually given daily for a consecutive series of twelve. To aid the patient in retaining the enema for at least six hours, Lovibond (1946) said that he raises the foot of the bed on 8-inch blocks and has the patient lie in turn for half an hour each on his left side, back and right side, this drill keeps the patient recumbent but has no other particular value.

Chiniofon, which is the oldest of the three hydroxyquinoline derivatives employed in amebiasis, was formerly also much used by mouth in 4 grain (0.25 gm.) pills, giving four such pills three times daily with meals for eight days; however, since this type of therapy often increased the diarrhea and caused a scalding sensation during defecation, it is no longer frequently employed. Direct toxicity from the rectal employment of the drug is not reported; it is not to be given parenterally

Diodoquin.—This drug is usually given by mouth following the emetine and chiniofon course: three tablets, each containing 3⅕ grains (0.2 gm.) three times daily for twenty days. D'Antoni (1943) gave two-thirds the adult dosage to children of six to eleven years. Diodoquin, like chiniofon a hydroxyquinoline derivative containing iodine, has a very good record regarding toxicity, though Morton (1945) reported two patients in a series of seventy-eight in whom attacks of abdominal pain, diarrhea and headache seemed to be chargeable to the drug, and David (1945) and Silverman and Leslie (1945) one and two cases, respectively, in which diodoquin was held responsible for dermatoses

Vioform.—This drug, like chiniofon and diodoquin, is a hydroxyquinoline derivative containing iodine. It is nowadays principally given in the form of enteric-coated capsules, 7½ grains (0.5 gm.) twice daily for ten days. Lewis (1946), treating a large group of patients most of whom had returned from the Pacific, including the China and India-Burma theaters, found this a most excellent drug. The toxicity of vioform is apparently quite low, and Lewis found that the powdered form, used rectally as 200 cc. of a 1 per cent suspension on alternate nights for five doses, was not irritating.

Carbarsone.—This drug has been found to be vastly superior to treparsol, acetarsone (stovarsol), or any of the other arsenicals in the treatment of amebiasis. It does not, however, seem to have held its own very well ag

the hydroxyquinolines (chiniofon, diodoquin and vioform) and is used by men of vast experience nowadays only when these other agents are not available. Carbarsone is given in a dosage of 4 grains (0.25 gm.) in capsules twice daily after meals for twelve days. The drug may also be satisfactorily used by rectum. A cleansing soda enema is followed in one hour by instillation into the rectum of 200 cc. of warm 2 per cent sodium bicarbonate solution *containing 1 per cent carbarsone*, 3 grains (0.2 gm.) of sodium amytal having been previously given by mouth to insure sleep and facilitate retention of the enema. If the enema is expelled before morning the treatment is repeated on alternate evenings until at least five enemas have been retained over night. Such a course may replace, but should not be given at the same time as, a course of the drug by mouth. The drug should be withdrawn in patients who experience gastro-intestinal irritation, congestion of the respiratory tract, visual disturbances, jaundice, neuritis, pruritus or skin eruptions; frequent examinations should be made to detect enlargement of the liver or spleen or evidences of renal damage. *Mayer (1946) reported the case of a patient who* died of hemorrhagic encephalomyelitis thought to have resulted from carbarsone administration.

Repetition of Courses.—If the Army plan of treatment, as outlined earlier [illegible]

of thirty days which, if followed by the prescribed two weeks of waiting before initiating the final tests of cure, will give a grand total of forty days from initiation of treatment to its completion. If amebae are still found present at the time of the tests, or if symptoms have returned before the expiration of the two-week waiting period, the whole treatment may be safely gone through with again. As a matter of fact, if the patient arrives at the end of the thirty days' course of treatment and is still symptomatic, it is customary with many *men to start the treatment all over again at once since more than three weeks* will have elapsed from the time of the last emetine injection. In the treatment of recalcitrant cases of hepatic amebiasis, Klatskin (1946) found that two-week rest periods between courses of six grains of emetine seemed most suitable, improvement often continued up to two weeks after the drug was stopped and this period proved to be sufficiently long to prevent cumulative toxic effects, but it was found that when the interval was prolonged beyond two weeks in the presence of liver tenderness, leukocytosis or an increased sedimentation rate a clinical recrudescence frequently occurred. In a few of Klatskin's more acute cases the second and third courses of emetine were given at eight- to ten-day intervals with no untoward effects.

Diet, General and Nursing Care.—In the severe cases, with fever and prostration, the patient must be in bed and should receive frequent feedings of boiled milk, stale or toasted white bread, white rice, soft cooked eggs, gelatin and tea. Many of the writers on this subject since War II have expressed their sense of the importance of maintaining an attitude of cheerful-

infusions of dextrose and saline helpful in the beginning. If there is excessive frequency of bowel movements bismuth should be employed at once and paregoric may be given in 2-drachm (8 gm.) doses at two-hour intervals to

control colic. Occasionally it will be necessary to give a hypodermic injection of ⅛ grain (8 mg) morphine sulfate, or 1/30 grain (2 mg.) dilaudid, with 1/120 grain (5 mg.) atropine sulfate. Should a period of costiveness then succeed the diarrhea there is no harm in giving a cathartic. Tenesmus may accompany rectal ulceration, the following might be useful, as suggested by Fantus:

℞ Iodoform	℥iss	10 0
Olive oil	℥iv	120 0

Keep on ice Inject 1 tablespoonful into rectum every four to six hours.

After the disappearance of acute symptoms in the fulminating cases there is no need to keep the patient in bed; indeed, in average cases without prostration or fever he need never have been put to bed—*except during the period of emetine therapy, when experience dictates caution because of the cardiotoxic nature of the drug* In building up the diet one should bear in mind that this patient will require smoothness combined with high protein and low carbohydrate; many observers have also attested the value of richness in vitamins. The following will meet the daily requirement pretty well for average activity:

Breakfast

Cooked cereal with cream but *very little* sugar
2 soft-cooked eggs
3 slices bacon
1 or more slices toast, or white bread, with much butter
Tea preferably for its astringency but coffee is permissible; again little or no sugar

Luncheon and Dinner

Lean cooked meats, generous portions
Baked potatoes or rice, much butter
White bread and butter
Milk as much as desired
Gelatin dessert, cream but no sugar
Tea or coffee if habituated

Raw fruits had best not be allowed for quite a while but the strained juices may be taken unsweetened and in much moderation; no leafy or vegetable salads. Work sugar and green vegetables back into the diet very slowly. Rogers (1933) stated that alcohol should not be taken by patients with amebiasis as it "strongly [illegible] ic hepatitis and liver abscess."

Hu[illegible] pa[illegible] [illegible]lescent or chronic carrier [illegible] of the disease is not the acutely ill [illegible] of the cysts, it is nevertheless desirable to treat the excreta and bedclothes in the acute stage much as is done in typhoid fever, attendants must also look scrupulously to the cleanliness of their hands.

PROPHYLAXIS

Dietary Precautions.—Brief sojourners in the tropics where the incidence of amebiasis is highest should endeavor to eat only thoroughly cooked foods and drink only boiled water or bottled beverages that are known to have been sterilized. But this is difficult of accomplishment and of course does not afford protection against subsequent and extraneous contamination by food handlers and other carriers.

taste; usually a crystal (or a *very* small pinch if in powdered form) of the "hypo" will suffice. For purification of larger quantities, 1 teaspoonful of hypochlorite should be used per gallon of water. When using canteens in the Army during War II, two halazone tablets were considered sufficient to kill cysts unless the water was turbid or colored, in which case four tablets were used, thirty minutes contact being allowed before consuming the water. One should add, I think, that Brady *et al.* (1943), after reviewing their own studies and those of others, were none too sanguine about the protection afforded by the chlorination of raw water. Becker *et al.* (1946) also felt that the method was undependable. During War II, soldiers often objected to the taste imparted to water by the issue chlorine tablets; the U.S. Army is experimenting (Trop. Med. News, 4, 11, 1947) with a new tablet of triglycine hydroperiodide that liberates less unpleasant iodine into the water.

Drug Prophylaxis.—Of all the drugs, diodoquin seems best suited for prophylactic use since it does not give rise to disagreeable symptoms and is highly effective. The same dosage is used prophylactically as therapeutically Craig (1940) said that it should be employed for twenty days even though the region is left before the expiration of that period; if the visit is longer than twenty days the course may be repeated after an interval of a week.

ANTHRAX

(Woolsorters' Disease, Malignant Pustule)

Anthrax is an acute infectious disease of animals, especially herbivora, caused by *Bacillus anthracis*. It is transmissible to man, in whom it appears either in the cutaneous, pulmonary or gastro-intestinal form. Workers in hide, hair, bristles, wool, horn, and bone are particularly susceptible, but it may be contracted by butchers, veterinarians, farm laborers, and others in contact with animals; Pinkerton (1939) reported a case contracted through pelting an infected mink. The disease is also occasionally contracted from an infected shaving brush. The incubation period is usually three to five days but may be as short as twelve hours or as long as two weeks. The pustule and edema of the cutaneous form are usually of a distinctive character, but there is often in the beginning considerable disproportion between these local changes and the amount of constitutional disturbance as evidenced by fever, rapid pulse and malaise. Consciousness to the end being characteristic, the appearance of delirium—indicating meningeal involvement—is always an *ill omen*. The symptoms of the pulmonary and gastro-intestinal forms are not distinctive of the disease and thus the correct diagnosis is often made very late. There are usually about 100 cases of anthrax in man in the United States annually; Smyth (1946) said that three-fourths of these cases occur in tanneries or woolen mills. The mortality rate was formerly very high but the newer types of therapy have brought it down in recent years almost to zero.

Anthrax was described by Hippocrates (460–370 B C) in one of the books of Epidemic Diseases thought to have been the authentic work of the Coan master, and it appears to have been well known during the period (732–1096 A.D) of Arabian and Jewish ascendency in medicine, but it is of interest to note that Galen (131–201 A.D) mistook Hippocrates' description as applying to erysipelas. The strange periodic malady of the middle ages, *malum malannum*, may have been anthrax, which is known with certainty to have been epidemic in the early seventeenth century. I believe the first complete treatise on the disease was that of Chabert, in 1780 Davaine discovered the organism in 1850, Koch demonstrated his cultures in 1876, Pasteur produced a preventive vaccine in 1880, and Sclavo, in 1895, offered the first of the serums which have since been widely used in therapy.

THERAPY

Local Treatment.—Other than the application of warm boric acid compresses, or of merely sterile gauze to collect the secretions, and the simple incision of an abscess if it forms, it is nowadays considered that nothing should be done locally except to put the part at rest. Koschucharoff (1938) considered both incision and excision contraindicated on the basis of much experience with anthrax in Bulgaria, he stated that thermocautery might arrest the process if employed in the very early superficial stage but he also felt that there were many reasons operating against its routine employment. Most authorities agree that excision should not be done because of the difficulty of accurately defining the area to be excised and especially for the reason that general dissemination of the malady may be hastened by the manipulations Enrich (1933), discussing his treatment of 340 cases in the badly infected Bradford district in England, said that the results have been much better since the abandonment of excision in all cases except those in which the pustule is very small and on a site notoriously apt to favor rapid extension, such as the neck, but he insisted that a limb should be fixed by splints and pillows or the head held in position by a towel carried across the forehead and fixed beneath sandbags. Lucchesi and Gildersleeve (1941), in the United States, followed a strictly "hands off" policy in their treatment of sixty-seven patients without a fatality; so too did Gold (1942), who lost only one of his sixty patients, the fatal case having been inadequately treated systemically, Smyth (1946), in an authoritative review, also supported this policy.

Penicillin.—At the time of writing I have seen the reports of forty-eight cases of anthrax treated with penicillin and it seems from the nature of the response that this new agent is certainly going to supersede all others The largest series was one of twenty-five consecutive cases reported by Ellingson *et al.* (1946) In most of these cases dressings kept moist with penicillin in saline solution (1000 units per cc.) were applied to the lesions for seven days and the intramuscular penicillin therapy was continued until the following criteria were met (1) edema had begun to recede; (2) cultures from lesions were negative for *B anthracis;* (3) systemic symptoms had subsided; and (4) lesions were dry. All the patients recovered uneventfully in spite of the fact that the organism was isolated from the blood stream in three of the patients prior to treatment Viable anthrax bacilli disappeared from the lesions in twenty-four hours or less in twenty-two of the cases and fourteen of the patients showed only slight systemic symptoms or none at all However, the

BLACKWATER FEVER

This syndrome is characterized by sudden onset with a rigor of chill and high fever, vomiting, jaundice, oliguria and finally anuria, usually severe upper abdominal and loin pain, enlarged and tender spleen, hemoglobinemia, methemalbuminemia in severe cases, often some degree of hyperbilirubinemia, hemoglobinuria, albuminuria, rapidly progressing anemia involving hemolysis of both parasitized and unparasitized cells, and a high death rate. There have been many speculations with regard to the causation of blackwater fever—for example, that it is a plasmodial infection complicated by some other parasite, such as Bartonella, or by an unknown virus; or that malaria with a tendency to blackwater has a different etiology from the ordinary form of the disease and may be caused by a specific plasmodium such as the *Plasmodium tenue* Stephens; or that several anophelines may be grouped into the single species *Anopheles funestus*, which is capable of modifying the malarial parasites so as to make them more apt to provoke blackwater. However, everything revealed in most of the careful studies of the occurrence of blackwater fever—such as the painstaking work of Whitmore in the West Indies and Central America, and of many others in Africa, India, and elsewhere—supports the belief that blackwater fever is a bizarre manifestation of *P. falciparum* infection, though also occurring in rare instances in association with infections by *P. vivax*, *P malariae* and *P. ovale*. There are regions thoroughly saturated with falciparum malaria in which blackwater fever is not seen. Where prevalent it is usually the newcomers—and not always only white newcomers, a fact thoroughly substantiated by Burkwall (1943)—who are attacked; returning sojourners from malarious lands sometimes come down with it also even though they may not previously have had a typical malarial attack. The direct cause of the hemolysis has not yet been established, but the studies of Maegraith *et al.* (1943) produced interesting evidence of the ability of human tissues to lyse erythrocytes and the presence in serum of a factor which inhibits this lysis, the titer of the latter factor being reduced in blackwater fever; Ponder (1944), and Bruckmann and Wertheimer (1945), have confirmed these findings at least so far as the lytic effects of tissue are concerned. Upon the other hand, Foy *et al.* (1945) concluded that the fundamental factor is probably extra-cellular since they found that cells from a blackwater fever patient were equally readily destroyed in a normal circulation and that the plasma from an actively

suggested the development of a hemolysin as the result of plasmodial invasion of the erythrocytes

THERAPY

... nd azotemia that occur in black-
... e of the renal tubules with the
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... locked, but we are still very far
... kage occurs. Whether the liberation
... n itself a harmful thing cannot be

said to have been decided as yet for there are experimental evidences on both sides of the question. As the result of an exhaustive review of the subject, Foy *et al.* (1943) concluded that the kidney changes result from extrarenal factors such as diminished blood volume, dehydration, and reduced circula-

anoxia is the result of hemolysis which we do not as yet know how to check.

Army Malaria Research Unit in 1945.

The administration of fluids to the patient is certainly rational, but since vomiting usually precludes the use of the oral route, frequent small retention enemas of normal saline, or the introduction of saline by proctoclysis or by intravenous infusion, must be resorted to, the addition of 5 to 10 per cent of dextrose will aid in sustaining the patient and combating acidosis

There is no evidence that oliguria and anuria occur more frequently in patients with acid urine than with alkaline, in fact, Foy and Kondi (1941) showed that anuria develops frequently in patients who have had only a small amount of hemolysis and passed alkaline urine and that it may fail to develop in patients in whom there has occurred considerable hemolysis and who have consistently passed acid urine Nevertheless, the use of alkalis has dominated the treatment of blackwater fever for a good many years. Smith and Evans (1943) went so far as to advocate the intravenous administration two or three times daily of 20 cc. of 2 molar or 3 molar solutions of sodium lactate, despite the fact that these solutions cause thrombosis of the veins.

of its prevention of intravascular hemolysis, but Dacie and Murgatroyd (1943) trenchantly remarked that the assumption of inhibition of hemolysis in blackwater fever as a result of the small changes in erythrocyte fragility produced by alkalosis is not warranted in the present state of our knowledge.

The application of hot fomentations to the kidney region is said to be sometimes helpful in anuria and often analgesic

Combating Anemia.—Smith and Evans (1943) said it has been calculated that a man may lose the equivalent of four to six pints of blood by intravascular hemolysis in thirty-six hours in blackwater fever. Red cells transfused to the patient are destroyed just as readily as the patient's own cells However, Blackie (1937), who gave the subject careful study over a period of five years in Southern Rhodesia, concluded that transfusion is an important life-saving measure if instituted early and repeated until there is evidence of active erythropoiesis, he believed transfusions to be contraindicated in toxic anuric cases, but Maegraith (1946) felt that the risk of lysis must be taken if the red cell count is reduced to 1.5 million per cu mm. Smith and Evans gave up the use of transfusions in the first two days because of the

frequency of severe reactions, and they stated that when giving a transfusion in blackwater fever it is probably best to start by giving only twenty drops in the first ten minutes, after which the transfusion may be proceeded with more quickly. Maegraith stated that because of the increase of agglutinins in the plasma, grouping before the transfusion is not in itself sufficient and that the donor's corpuscles should be cross-matched with the patient's serum and vice versa. Loutit (1943) said that in two cases he had good results from repeated transfusions with concentrated red cell suspensions without reaction.

In the after-treatment of the severe anemia the use of both iron and liver preparations is rational.

Nursing Care.—All agree that because of the rapidly developing and severe anemia there quickly arises great danger of circulatory failure of the type for which we unfortunately have no satisfactory remedial agents. The best weapon is prevention, which takes the form not only of having the patient in bed but keeping him quietly there by allaying his apprehension and restlessness with sedatives (see Insomnia), indeed, according to Gregory (1944), the immediate intramuscular injection of 10 grains (0.6 gm.) of phenobarbital sodium, possibly followed by a dose half this size in two hours, is the most important item in the therapy of blackwater fever, which is very interesting if true—in fairness it should be stated that Gear (1946) found it quite logical that sedation of this sort would be remarkably effective in reducing splenic contraction and thus preventing flooding of the circulation with the autolysins that he holds responsible for the syndrome.

Antimalarial Drugs.—There is considerable evidence that the taking of large amounts of quinine in the treatment of repeated attacks of malaria may be the factor that precipitates blackwater fever. Maegraith said that in the West African Command in 1941–43, hemoglobinuria developed in a high proportion of cases of falciparum malaria during oral quinine therapy; regarding this same Command at a later period, Skipper and Haine (1945), quoting Findlay, said that the incidence of blackwater fever diminished considerably after the substitution of atabrine (mepacrine, quinacrine) for quinine in the treatment and suppression of malaria. Subsequent experience has certainly demonstrated that atabrine may be safely used, but since the organisms usually disappear quickly from the blood-stream when the blackwater attack begins there is not a pressing need for the use of an antimalarial agent during the first few days. A week to ten days after hemolysis has ceased, a course of quinacrine (see Malaria) should be given to prevent a malarial relapse; Murgatroyd (1943) said that if quinine has to be used it should be given in a beginning dose of $\frac{1}{2}$ grain (30 mg.) three times daily and gradually increased up to 10 grains (0.6 gm.). Fairley and Murgatroyd (1940) reported a case in which the capacity of quinine to produce blackwater fever appeared to be definitely related to persisting malarial infection, since after the apparent cure of the malaria quinine administration entirely failed to induce hemoglobinuria.

BRUCELLOSIS

(*Malta Fever, Mediterranean Fever, Undulant Fever*)

Brucellosis is an infectious disease caused by *Brucella melitensis*, *B. abortus*, and *B. suis*, the clinical manifestations being probably identical no matter which of these organisms is the infecting agent. *B. melitensis* is harbored by goats, apparently without being harmful to these animals, and the infection is contracted by the human being through direct contact with the animal or through ingestion of its milk. The disease is endemic and epidemic in the Mediterranean littoral and elsewhere in the world where raw milk from infected goats is consumed Where prevalent, it is a difficult disease to stamp out for the reason that the goat is a profitable animal in these regions and the sterilization of its milk renders it decidedly objectionable in taste. Besides, the goatherders in the rural districts refuse to believe that such a disease exists, perhaps because of their own immunity owing to a gradual vaccination.

Owing to the increasing prevalence of the disease in the United States and other countries where goat's milk as the carrier could be practically ruled out, and prior to the demonstration by Jordan and Borts (1946) that hog-borne *B. melitensis* brucellosis is endemic in the State of Iowa, it became necessary to search for some other organism capable of causing the malady. This quest was rewarded by the discovery that *B. abortus* and *B. suis*, the organisms responsible for the infectious abortion of cattle, sheep and hogs, were also the etiologic agents in human brucellosis in many parts of the world. This form of the disease, as contracted through ingestion of insufficiently pasteurized cow's milk, may of course appear endemically or in small epidemics; there are also many contact cases in farmers, butchers, sausage makers and veterinarians; work with this organism in the laboratory is very dangerous. Transmission from man to man has not been unequivocally demonstrated, though the organism has been recovered from mother's milk and even, though very rarely, from the sputum; according to Spink and Hall (1945) it remains viable in refrigerated butter for four months and in refrigerated milk for ten days. It is generally considered that one attack of the disease confers lasting immunity, and immunization of those frequently exposed doubtless often takes place without the development of a recognizable attack. Brucellosis is of infrequent occurrence in young children

A patient with persistent or intermittent high fever accompanied with great fatigue and joint or muscle pains, with sweating and a palpable spleen, may have brucellosis, but tularemia, malaria, and a number of other acute infectious diseases must be ruled out, for brucellosis is inclined to be protean in its manifestations. Rheumatic symptoms, salpingitis, orchitis and epididymitis are of frequent occurrence, middle ear disease, and pharyngeal

cystitis and focalized hepatitis, hematopoietic damage, specific bronchopneumonic consolidation, various dermatoses, and numerous other symptoms or

grab-bag known as "neurasthenia"—is being increasingly recognized, this

entity has come to be one of major importance indeed. The usual incubation period is two weeks in the Mediterranean cases but it varies from slightly less than one week to several months, here in the United States it is thought to be ten to fourteen days in most cases, with extremes of five to twenty-one days. The course, even of the milder among the cases that are positively identified, is very protracted, mortality is in general fairly low (3 per cent in the United States, according to Huddleson *et al.*, 1939, and only about 1 per cent in the more recent opinion of Carpenter, 1943), but occasionally the attack may be of a quite malignant nature.

According to Calder *et al.* (1939) the most striking feature of the blood picture in their 271 patients was active lymphocytosis with an unusually high proportion of immature lymphocytes in the peripheral blood; Spink and Hall (1945) confirmed the finding of a relative or absolute lymphocytosis in *B. abortus* cases in the United States, and Castaneda and Guerrero (1946) in *B melitensis* cases in Mexico. In Calder's series the coagulation time was also prolonged and clot retraction was imperfect. I think it is now the consensus that none of the three tests—the intracutaneous, agglutination and opsonocytophagic—used individually is of specific diagnostic importance without supporting information from the other tests and from history and examination. Any of them may be positive in asymptomatic cases (although this is rarely true of the blood agglutination reaction in high titer) and any or all may be negative in cases proved by culture of the organism. Harris (1947) evaluated these tests as follows: if the intracutaneous and agglutination tests and the culture are all negative, we do not know whether or not the patient has ever had brucellosis and therefore the opsonocytophagic test, which merely indicates the degree of opsonic activity of the blood toward Brucella, usually has no interpretable diagnostic significance However, caution is necessary in evaluating the result of the tests since the presence of specific opsonins is unlikely except as a result of past or recent infection. If the intracutaneous test is positive it can be accepted if the patient has an old or recent infection of undetermined activity; a violently reacting intradermal test is unlikely except in fairly recent infections or in the presence of a history of skin contact with brucella organisms. If, in the presence of symptoms referable to brucellosis, the positive intracutaneous test is accompanied by a low opsonocytophagic test, it is presumptive evidence that the patient has not recovered from the old infection; if accompanied by a high opsonocytophagic test the patient usually may be presumed to have recovered from the infection. Harris feels that it is usually unwise to try to interpret the three tests individually but that they are best used as a battery. Positive culture from blood, urine, feces, sputum, bile, synovial fluid or other exudate, discharge or tissue, alone is definitive, but there is a reasonable expectancy of recovering the organism only in the presence of acute infection, especially when the *abortus* species is the etiologic agent.

THERAPY

The symptomatic treatment is such as would ordinarily be instituted in typhoid, influenza, acute arthritis, etc. In describing the handling of a small milk-borne epidemic of the disease, Borts *et al.* (1943) stressed the fact that bed rest during the course of the acute illness and for ten days to two weeks after the temperature has returned to normal is probably the best assurance against extended illness. In addition to bed rest and symptomatic treatment

upon to influence favorably all the cases in which it is used. It seems to me that one should view with the utmost skepticism all reports of cure based upon only a few months of observation, for brucellosis is a disease with many remissions and it would seem that five years of freedom from all manifestations of illness should be required for substantiation of all claims for specificity.

Vaccine.—It would seem that whatever is attainable with vaccine therapy is attributable to the general foreign protein reaction and is therefore obtained as easily with typhoid as with brucella vaccine, the latter is no longer Council-accepted. Nevertheless, Harris, in 1946, still stoutly championed the heat-killed *B abortus* vaccine for the treatment of chronic cases, but it seems to me that his statement of efficacy was somewhat equivocal—"When it becomes possible to review every case history and to interview a large per-

of vaccine, using it without optimism only after sulfonamides and hyperthermia had failed They determined the sensitivity of the individual to the vaccine as measured by an intradermal test, and then, with the object of provoking a moderate systemic reaction with each injection, gave the vaccine

prepared by Foshay were very remarkable either; in some cases he thought intravenous administration of nicotinic acid was additionally helpful.

Hyperthermia.—Prickman *et al* (1938), at the Mayo Clinic, treated a small group of patients by inducing fever in the Kettering hypertherm; they felt their best results were obtained in acute and subacute cases, Phalen *et al.* (1942) recorded the satisfactory treatment of three cases of brucellosis spondylitis. Levitt (1943) wrote that hyperthermia had been employed with indifferent results at the Cook County Hospital, but Spink and Hall (1946) recorded satisfactory results in four of five chronic cases and felt that this type of therapy merited further consideration

Brucellin.—Huddleson has been the chief advocate of a filtrate of a broth culture of the three strains of brucella. Benning (1946) reported great improvement in about 61 per cent of the seventy-eight patients he treated, but one must view this report with some skepticism for he based his diagnoses largely upon the intradermal test alone (which actually determines only the presence or absence of cutaneous sensitivity to brucella protein) and accepted as evidence of recovery the freedom from symptoms for only about six months. In a limited experience with brucellin, Harris (1946) found it sometimes to have a rather pronounced deleterious effect. If there is no marked systemic reaction in twenty-four hours to the preliminary intradermal injection of 0 1 cc. of this material (brucellin), Huddleson gives 0.2 cc. intradermally and 0 8 cc intramuscularly in the afternoon or evening, this induces systemic reaction and he likes to induce such reactions three or four times at intervals

of three days. Huddleson (1939) reported 500 cases treated by himself and a number of widely scattered physicians and considered the results favorable. Borts *et al.* (1943) used brucellin in all seventy-seven of the patients involved in the epidemic reported by them, giving the injections at intervals of three to five days until three doses had been given after the febrile reaction had ceased to be produced. The average number of injections was fifteen, which means that their patients were stuck fifteen times at intervals of three to five days with the avowed purpose in all save the last three doses in each instance of causing a febrile reaction—to my mind the results would have to be extremely good to justify that sort of treatment, but nothing very specific was said about the results in Borts' report. Spink and Hall (1945), though they had had no experience with brucellin, said they did not consider it the agent of first choice in an acutely ill patient having bacteremia, even though he was sensitive to the material.

Whole Blood Transfusion.—Quevli and Nelsen (1932) were very favorably impressed by their results with one or two transfusions by the usual method in nine of their ten cases, but since their report a good many transfusions have been given without setting any therapeutic rivers afire.

Human "Immune" and Convalescent Serum.—Poston and Smith (1936) injected human immune serum intraspinally in two meningitis cases; the dose of 16 cc. was repeated three times on alternate, once on successive days. The serum was obtained from an individual who had been immunized eight years previously to several strains of brucella with no subsequent injections of vaccine. In 1938, Poston and Menefee gave 250 cc. of citrated blood intravenously from this same donor and thought the patient's rapid improvement was initiated by this treatment Harris (1946) described satisfactory improvement apparently induced in a patient to whom he had given 500 cc. of citrated whole blood from another patient who had apparently recovered. Of course ordinary convalescent serum has been tried numerous times according to methods similar to those employed in measles and other diseases.

Antiserum.—Goat antiserum, developed by Foshay and his associates, was reported upon by them (Wherry, O'Neil and Foshay, 1935) as employed in twenty-six cases by widely scattered physicians. Flippin (1938) used a bovine serum in five cases These serums were thought to have been useful, but they no longer seem to be available.

Sulfonamides.—All of the older chemotherapeutic agents have been tried and are now no longer used. The sulfonamides got off to a good start but latterly they have found few champions. Harris said that they are unlikely to cure either the acute or chronic forms of the disease; sulfadiazine was ineffective in the eleven acute cases in which its use was persisted in by How *et al.* (1947) for twenty to thirty days.

Penicillin.—Despite the effectiveness of penicillin against brucella *in vitro* there is no evidence in the record indicating that it has any value in the treatment of the disease in man.

Streptomycin.—In an authoritative report the committee under Keefer (1946) described the results in the forty-five cases that had been treated up to that time. Thirty of the patients showed a decrease in fever under treatment and in fifteen there was no effect on the course of the disease. Of the thirty patients with a decrease in fever, twenty-nine were followed for three to eight weeks without relapses. Of the fifteen patients who showed no improvement ten received only 2 gm. of the drug daily; Keefer *et al.* felt that the

minimum dose in brucellosis should be at least 4 gm. daily for fourteen to twenty-one days. It seems fairly certain that streptomycin is not going to work wonders in brucellosis; indeed there are cases on record in which bacteremia persisted despite the presence in the blood serum of streptomycin levels many times greater than those required to kill the organism in the test tube.

Surgery.—There is a growing belief that brucella tends to become imbedded in foci difficult to reach with drugs. A good many gallbladders have been removed for this reason, but it is not evident that many cures have resulted. Now there begins to be talk of the spleen as the principal site in which the organism resides, and there are records of a few good results following splenectomy. But heaven help us when the craze begins for the removal of the spleen of everyone who has a positive intradermal test for brucella!

CHICKENPOX

(Varicella)

Chickenpox is an acute infectious and highly contagious disease of unknown etiology, which attacks nearly all children at some time during their early years. Several serious students are at present attempting to show a causal relationship between it and herpes zoster, but they have not yet succeeded.

as this glib statement would indicate!) by the fact that it begins on the back, or some part of the trunk whence it spreads to the whole of the body, including the scalp, but is seen on the face and palms and soles only occasionally, and then to the extent of only a few lesions; that several stages of the eruption may be seen at one time, to wit, erythematous maculopapules, clear vesicles, clear vesicles surrounded by an erythematous corona ("a dewdrop on a rose petal"), turbulent vesicles, somewhat pustular vesicles, and crusted vesicles; by the fact that these vesicles are more nearly unilocular than in smallpox (collapsing more completely after a single needle puncture) and that they are more irregular in outline than the smallpox vesicle and are not umbilicated. Anomalous forms of the rash are occasionally seen Lucchesi

The incubation period varies from four to more than twenty days but most cases develop twelve to fourteen days after exposure. One attack practically always protects for life; therefore, since most mothers are immune and transfer the immunity placentally, chickenpox in the newborn is rarely seen So far as is known to me there is no racial immunity to chickenpox. In 1936 the disease was severely and fatally epidemic among the natives in French

Cameroun, and Mumford and Mohr (1944) stated that it ha highly fatal epidemic disease in the Marshall Islands in 1887.

Chickenpox was first described by Ingrassias (1553), but th of the early treatises is that of Heberden (1767), which contai illustrations. Attention was first attracted to the possible relati disease to herpes by Bokay in 1892.

THERAPY

Chickenpox is constitutionally a mild affair and usually require ment. The eruption occurs during two to five days and usually mo scabs are off in a week but sometimes a few cling to a tough centra several weeks After-scarring is very infrequent. For control of the recourse may be had to the measures employed in smallpox. Bullo Wishik (1935) tabulated complications in about 5 per cent of 2534 c hospital but the incidence is certainly lower in home-treated cases. The serious though very rare occurrences are doubtless massive skin gangrene the form known as varicella pustulosa in which most of the pocks bec furuncles or solitary abscesses In these cases, of course, sepsis or bronc pneumonia is much to be feared. The lesions should be frequently cleans with boric acid solution, or perhaps it is preferable to immerse the patient f fifteen to thirty minutes several times daily in a warm bath containing level teaspoonful of potassium permanganate to four gallons of water. The easiest way to prepare such a bath for the first time is to fill the tub to the desired point from a pail of known capacity. It is well to have the tub washed out afterward to prevent permanent staining, with a solution of ½ ounce of oxalic acid (poisonous!) to the quart of water, rinsing well afterward. I have seen no record of the employment of the sulfonamides or penicillin in such cases. Complications of the nervous system, such as encephalitis and enceph-alomyelitis, have been reported but are extremely rare and usually of good prognosis, though Waring *et al.* (1942) reported the case of a forty-year-old male who died with complicating pneumonia, encephalitis and nephrosis. Gangrene and extensive necrosis around the site of the pocks is a very serious but fortunately extremely rare complication.

PROPHYLAXIS

Since chickenpox is so absolutely benign in the very young it seems many observers that it would be the part of wisdom deliberately to allow youngsters to contract the disease, and I share that opinion. However, the general professional orientation is toward prevention in this as in most infectious diseases.

Vaccination.—The vaccination of exposed individuals with the contents of chickenpox vesicles was introduced in Germany by Kling in 1918, but it has not been the consensus that it has much protective value; however, a favor-able report (von Gulácsy, 1933) still appears now and then. The contents of a fresh vesicle, drawn up into a capillary tube, are introduced by the punc-ture or intracutaneous injection methods in all details precisely as in small-vaccination. The "take" occurs between the eighth and thirt papule, vesicle, crust and possibly scar

Convalescent Serum.—The studies of Go at pooled whole convalescent

one month of the appearance of the donor's eruption and stored not longer than four months, the dose being 4 to 10 cc. intramuscularly and severe reactions apparently not occurring However, Lewis *et al.* (1937) failed to find such convalescent serum of the least value in protecting against the disease, and the several studies of McGuinness (1943) and his group indicated no higher value for reconstituted pooled lyophile serum.

COCCIDIOSIS

Human infestation with *Isospora hominis* is a little understood occurrence, some investigators indeed doubting the pathogenicity of the organism for man. The definitive paper is still that of Magath (1935), in which was summed up the experience following War I Since War II additional cases have been reported, Maldonado (1946) bringing the total up to 297. The infestation is apparently world-wide in distribution in tropical and subtropical regions. The cases are found sporadically, never epidemically, and since allied if not identical organisms are found in many animals it is assumed that a reservoir host explains the low incidence in man The oocysts are found in the stools and are assumed to be ingested in food and drink. Most of the reported cases have been associated with some other intestinal disorder which primarily brought the patient under observation, a few asymptomatic cases have been reported in which this organism alone was isolated, and in still fewer instances the organism alone has been held responsible for mild dysenteric symptoms such as abdominal discomfort, flatulence, slight diarrhea, weight loss and lassitude. It has been assumed that in these latter cases the oocysts have invaded the mucosa of the small bowel and formed small bottle-shaped abscesses there from which after schizogony and sporogony, new cysts are poured into the lumen of the bowel However, there is not in existence any fully reliable evidence to substantiate this assumption In one accidental laboratory infection a mild diarrhea occurred after an interval of six days and continued for five weeks, but Humphrey (1946) felt that in his three patients, seen on Okinawa, the incubation period may have been as long as ten to twenty days; infection in these three cases was apparently associated with a moderate eosinophilia and one of the patients had a fever early in the course of the disease.

THERAPY

Anthelmintics and amebacidal agents have been used in treatment of most of the cases but it is impossible to assess their value since this infection in man is almost certainly self-limited Of the more recently reported cases, that of Albritton and Fitzwater (1945) was cleared following two treatments with tetrachlorethylene, Maldonado's patient was given fuadin; and the patient of Kiskaddon and Renshaw (1945) became free of coccidia while being treated with sulfasuxidine for another purpose.

fashioned Dover's powder (powder of ipecac and opium, N.F. VII) used very much to be employed for this purpose; the ordinary single dose (in capsule) of 5 grains (0 3 Gm.) Diehl (1933) found may be safely and well increased to as much as 15 grains (1 Gm.), but since he observed that powdered opium alone in equivalent dosage was equally valuable he concluded that the diaphoretic action of the ipecac was unimportant. Furthermore, out of his apparently well controlled study of the effects of opiates on the common cold emerged the fact that a combination of ¼ grain (15 mg) of codeine sulfate and ¼ grain of papaverine hydrochloride was more valuable than any other preparation in inducing prompt decrease or complete disappearance of the nasal discharge and congestion, and this without the unpleasant dryness that usually occurs when atropine is used for this purpose. Accompanying laryngitis, pharyngitis and tracheitis were not materially relieved. The following is his dosage scheme in terms of single capsules each containing the two drugs as above stated:

75 to 99 pounds	1 after breakfast; 2 at bedtime
100 to 129 pounds	1 after breakfast; 3 at bedtime
130 to 169 pounds	1 after breakfast; 1 after lunch, 3 at bedtime
170 pounds and over:	1 after each meal and, depending on weight, 3 or 4 at bedtime

Unpleasant symptoms such as nausea, dizziness, headache and fainting were infrequent accompaniments of this medication; addiction to either of the drugs [illegible] is much used in the [illegible] nd capsule; copavin [illegible] which contains one-half grain (30 mg.) of codeine sulfate, one-half grain (30 mg.) of papaverine hydrochloride, one-quarter grain (15 mg.) of aloin, and 20 grains (1.3 gm.) of sodium salicylate.

Another method of relieving the feeling of fulness in the head is to cause the patient to breathe an atmosphere that is saturated with moisture. A teaspoonful of the following inhalant may be vaporized by pouring scalding water upon it in a previously heated cup, with his head low over the cup, and a large towel enclosing both, the patient breathes with mouth open. Sometimes the feeling of stuffiness is only increased by such a steamy inhalant; exposure should be avoided for an hour after its use. The housewife will be grateful if forewarned that both the cup and spoon are very difficult to clean after their employment for this purpose.

℞ Oil of pine needles	ʒiv	15.0
Tincture of benzoin to make	℥iv	120.0

If desired, creosote (½ drachm, 2 gm.) may be added to the above, but as it is a mixture of phenols there is some reason to believe that if used too freely it may cause some damage to the kidneys. For bedridden patients, Means and Lerman (1932) found it convenient to place the above ingredients in an ordinary teakettleful of boiling water on a chair beside the bed; a length of large rubber tubing is stuck onto the spout and the patient takes the free end into his mouth, thus getting the full effect of the medicated steam without having to put his neck into an uncomfortable position.

Nowadays the benzedrine (amphetamine) inhaler is much employed for the relief of nasal congestion, but some patients react unfavorably with restlessness and secondary reactions of the mucosae. Kully (1945) referred to the "suggestive coincidence" that in a series of 640 of his patients with acute sinusitis 85 per cent had used nasal vasoconstrictors for several days prior to the onset of the sinusitis

For the relief of the substernal tightness and pain, a mustard poultice is frequently employed This is conveniently made by spreading between two layers of thin muslin a paste made by mixing equal parts of ordinary household mustard and wheat flour stirred together with warm water. Prepared plasters which are very convenient to use may be purchased at drug stores, but these too should be dipped in warm and never in hot water, for the irritant property in mustard is developed through enzyme action and the enzyme is killed by heat. Whether the prepared or home-made article is used, it should be left in place over the upper part of the sternum until the skin becomes quite red, which usually requires from fifteen to thirty minutes.

Combating Cough.—Among the expectorants ammonium chloride is probably the most certain in its action (but *not* if used as enteric-coated tablets). Some such preparation as the following, which contains approximately 8 grains of the drug to each teaspoonful, is usually effective if given every *two* hours:

℞	Ammonium chloride	ʒiv	15 0
	Syrup of citric acid	℥j	30 0
	Water to make	℥iv	120 0

[illegible]

satisfactorily supplements the action when used as a vehicle.

℞	Ammonium chloride	ʒiv	15 0
	Compound mixture of opium and glycyrrhiza (N F. VII)	℥iv	120 0
	Label 1 teaspoonful every two to three hours		

A sip of pineapple juice after ammonium chloride very nicely overcomes [illegible]

potassium iodide may be given in water every two hours, but bearing in mind the frequent occurrence of iodism, the interval between doses should be lengthened as soon as possible The syrup of hydriodic acid is well taken by children in doses scaled down from 1 drachm (4 0 gm) according to size and age However, bronchial irritation may be aggravated by the iodides. Syrup of ipecac is frequently used also The best dosage with which to achieve expectorant action without causing nausea is 5 to 8 minims (0.3–0 5 gm.) every two hours

℞	Syrup of ipecac	ʒiv	15 0
	Aqueous elixir of glycyrrhiza to make	℥iv	120 0
	Label 1 teaspoonful every two hours		

For a child, with its preference for sweets, the syrup of glycyrrhiza had best be substituted, or any of the other vehicles liked by children may be used: syrup of raspberry, syrup of tolu balsam (vanilla-like flavor), syrup of cacao

(chocolate flavor), syrup of cinnamon. Evidently the profession, at least in England, is very fond of the use of iodides and ipecac in cough, for when Alstead (1939) questioned their value he was very tartly reprimanded in a letter "to the editor" of the Lancet.

When it is felt that a full effective amount of an opiate should be incorporated in the cough mixture, some such prescription as the following may be written:

℞ Pantopon.	gr. iss	0 10
Syrup of cacao to make	℥iv	120 00
Label 1 teaspoonful every three hours (for adults).		

The pantopon is present here in 1/20-grain (3 mg.) doses Dilaudid in the amount of ½ grain (30 mg) could be substituted for pantopon; the teaspoonful dose would contain about 1/64 grain (1 mg.).

The following are satisfactory codeine prescriptions:

℞ Codeine phosphate.	gr. viiss	0 45
Ammonium chloride	ʒiv	15.00
Syrup of citric acid	℥j	30 00
Water to make	℥iv	120 00
Label· 1 teaspoonful every three to four hours.		

℞ Codeine phosphate.	gr iv	0 24
Elixir of terpin hydrate to make	℥iv	120 00
Label 1 teaspoonful every three to four hours.		

The first of these prescriptions contains approximately ¼ grain (15 mg.) of codeine phosphate, the other 1/6 grain (10 mg) per dose, it is well to bear in mind that elixir of terpin hydrate contains about as much alcohol as does whiskey. A larger amount of codeine may be needed, though Davenport (1938) found that in most instances in tuberculosis sanatorium practice the smaller doses suffice. Codeine is of course non-addictive and therefore may be safely used; I am not as yet convinced that the new substitute for codeine, hycodan, which Stein and Lowy (1946) found highly effective in the sedation of cough, has a sufficiently low addiction liability to justify its substitution for the older drug

Cathartics.—And now the question of the initial cathartic. I well remember my late professor of medicine as, with serious mien, he said to us many a time in class, "Gentlemen, I *always* prescribe calomel on the first visit," and then, with a sly twinkle in his eyes, "or on the second." And doubtless he did just that. But why? Certainly if a cathartic is to be used at all it had best be calomel, or at least not a saline, for Macht and Finesilver conclusively showed in both laboratory and clinic that the taking of a saline cathartic prevents the absorption, and therefore the effect, of other drugs taken simultaneously or quite some time later But why give a cathartic at all when we know the debilitating effect of a purge even in a well individual? Some time ago the following facetious letter, which has caused me much amusement, appeared in the Journal of the American Medical Association; I quote almost *in toto*:

"*To the Editor*:—I appeal to the fountainhead of medical knowledge for information on a subject of greatest personal and community importance Shall I take a physic? And shall I give a physic to practically all my patients? I have not taken a physic for nearly fifteen years and I am in perfect health. My intestinal exit operates as faithfully as the inlet, with an almost unvarying ratio of three to one. Traffic occasionally slows up a bit, and as a consequence terminal unloading

vinces me that I do far less cleaning out than they do, and when it comes to toning up a liver with

E O. Harrold, M. D."

Well, well! Smith and Baier (1939) put the matter to the test in a study at an Army post early in War II, employing castor oil and magnesium sulfate in 520 cases with 493 untreated controls (all patients having temperatures ranging between 100° and 102° F); they felt that the use of the cathartics actually prolonged the attack

Fluid Allowance.—As in all other fevers, water should be liberally given. The patient should take at least ½ tumblerful every hour while awake. It is often easier to induce the taking of this much fluid if it is given in the form of lemon- or orangeade. This fruit juice, since it is potentially alkaline, also helps to meet what is generall

the necessity to overcome aci

whether the effectiveness of "

clinical tradition, is not definitely answered so far as I am aware. A quarter-teaspoonful of sodium bicarbonate added to the glass of lemonade will help

rational basis.

Diet.—In the beginning, when the patient is feverish and feeling quite ill, he will likely be uninterested in taking more than the fruit juice referred to

above; if this is fairly well sweetened he is of course getting a bit of nourishment. Ideally, if the siege threatens to last a number of days, it would be well to have him drink a quart of milk (reinforced by about a half pint of cream if he will accept so much "richness") during the twenty four hours and offer him a couple of soft-cooked eggs and a small portion of cooked cereal at one or other of the usual mealtimes. See Index for an eggnog recipe. Later, in leading back to full diet, reduce the milk and add small amounts of bread and butter, lean cooked meat, and a bit of green vegetables or buttered baked potato if the aroma of that will tempt him. Occasionally a patient with grippe will develop a quite voracious appetite after a few days, a circumstance which we often meet by denying him all he wants because he is "lying inactively in bed," but Davis' (1934) studies indicated that perhaps in infants and young children at least our counsel of abstemiousness may not be so wise. In her work in a nursery in which, regardless of the height of fever, the youngsters were allowed to continue the choice of their foods during the course of colds and tonsillitis, she not only confirmed the well-known fact that appetite decreases twenty-four hours before there are any other signs of illness, but also observed that twelve to twenty-four hours before the fall in temperature or improvement in signs there was a sharp increase in desire for food. A child with high fever and several days' lack of interest in his food would suddenly sit up when his tray came in and eat heartily, with second and third helpings, of meat, potatoes and vegetables; no digestive disturbances resulted and convalescence followed predictably on the next day It is interesting also that regardless of their predilections when well, these children turned with enjoyment to raw beef, beets and usually carrots when recovering from acute upper respiratory infections.

Sulfonamides.—The ordinary uncomplicated cold runs a mild afebrile course and clears up in four to seven days. Though having no mortality associated with it and oftentimes not even greatly incapacitating the patient, it may nevertheless cause some measure of debility for a considerable period of time and therefore is of great economic importance. The more severe cold which is complicated by secondary bacterial infection involving the sinuses, the middle ear, the mastoid, and so on, is a serious matter indeed and therefore any agent which could be shown capable of preventing with fair regularity the bacterial complications of ordinary colds would be a welcome addition to our armamentarium. Sulfadiazine has had the most extensive trial in this connection, with results which will be discussed below.

Effect upon the Uncomplicated Course of the Disease.—The findings in three principal studies require to be recorded. Rusk and van Ravenswaay (1943), in an Army camp during War II, gave to 317 patients an initial dose of 3 gm. and subsequent doses of 1 gm. every four hours until convalescence was established or nonimprovement in protracted cases indicated that dosage should be stopped; acetylsalicylic acid, acetophenetidin and caffeine citrate were given to the 314 patients in the control group. No significant differences appeared, either in the length of the febrile period or in the period of hospitalization, in the two groups; and, very properly, the authors pointed out that the cost of the sulfadiazine treatment was approximately twenty times as great as treatment with simple analgesic capsules, a cost differential which would probably be much greater in civilian life. Cecil *et al.* (1944) followed seventy-two colds in sixty-six persons; forty-eight were treated with sulfadiazine 1 gm. three times daily by mouth for four days, while twenty-four

of the colds were untreated as controls They found that the clinical course of the treated colds showed no striking difference from that of the controls and therefore expressed themselves as opposed to the routine use of the sulfonamides in the treatment of the common cold. Siegel (1941), after a carefully controlled study extending over several years among highly susceptible institutionalized feeble-minded children, was able to say only "the illnesses were milder, on the whole, in the drug-treated groups than in the untreated groups, with the exceptions noted in outbreaks of uncomplicated infections presumably of viral origin and in sporadic infections during the period studied. The beneficial effects were attributed to the bacteriostatic action of sulfadiazine on the susceptible bacteria primarily or secondarily involved"—or, when the colds were of the ordinary uncomplicated sort, no advantage accrued from the use of sulfadiazine

Effect on Incidence of Complications—The principal study to be considered in this connection is that of Dolowitz *et al.* (1943), of the Johns Hopkins Hospital, who treated fifty-nine members of the nursing staff with sulfadiazine and left forty-four as untreated controls. They administered sulfadiazine by spraying the nose and throat eight to twelve times daily for three days and five to eight times daily for two or three additional days with a 2 5 per cent solution of sulfadiazine in 8 per cent triethanolamine solution. Some patients objected to the taste of this spray, others complained of the irritation it caused around the external nares (the latter said to be prevented by frequent application of cold cream and petrolatum), and about 3 per cent of the patients developed sneezing and increased rhinitis as a result of the use of the spray, however, Dolowitz *et al.* seemed firmly convinced that by using the drug in a spray rather than in the form of tablets to be swallowed they obtained a much better inhibition of the growth of organisms in the sprayed area. The results recorded in this study were the following: sinusitis in treated group 9.7 per cent, in control group 30 per cent, otitis media in treated group 1 8 per cent, in untreated group 4.5 per cent, laryngitis in treated group none, in untreated group 2 3 per cent; sore throat in treated group none that developed during treatment, in untreated group 10 per cent; cough developing during treatment in treated group 8 per cent, in untreated group 44 per cent. A more recent but much less detailed study was that of Faust and Simmons (1944) in one of the Army camps In this study 4 gm. of the drug were given initially by mouth and 1 gm. every four hours thereafter as long as seemed indicated. One hundred and thirteen patients were so treated and eighty-seven were given analgesic capsules and used as controls. The complications which developed in these two groups were bronchitis, tonsillitis, laryngitis, inflammation of the ear drum and sacro-iliac pain, and the average hospital stay of sulfadiazine-treated cases with such complications was said to have been 6.2 days while that of the untreated controls was 9.9 days.

Summary—I do not know what to make of the above evidence except the following. (a) that the routine employment of sulfadiazine will not affect the course or duration of an ordinary mild common cold; (b) that it will, however, to a considerable extent reduce the incidence of bacterial complications; and (c) that the cost of this therapy is an item of some importance. Cecil *et al.* stated that on the basis of their experience they would restrict the use of the sulfonamides to very few selected cases, such as those in which the history reveals an almost invariable and severe secondary infection following the

cold; and that would seem very good advice to follow under ordinary circumstances in peace-time civilian practice.

Penicillin.—Woodward and Holt (1945) used aerosolized penicillin in forty patients seen in the prodromal stage of the common cold and considered the results encouraging because the majority of the patients felt themselves to be improved in forty-eight hours; but this could well have happened also in a control group had they had one. Menefee and Atwell (1946) treated sixty-six patients but frequently felt it necessary to shrink the nasal membranes with one-fourth per cent neosynephrin before spraying in the penicillin. As far as they could determine the treatment had no effect on the course of the common cold, the failure of complications to develop means nothing since in this series, as in the above, there was no control group.

PROPHYLAXIS

Chilling of any portion of the body and excessive fatigue both probably lower resistance to infection and should be avoided, especially during the inclement months. Jarvis (1939) stated the belief that there is a type of individual whose respiratory tract does not adjust well to marked differences in temperature and that such persons should not sleep with the window open in severely cold weather. The crowding together of large numbers of people in closed spaces doubtless facilitates the spread of the common cold and ideally one should shun such crowds, but some fun must be had in life too and man is a gregarious animal. Regarding the more specific methods of prophylaxis the following may be said.

Bacterial Vaccines.—The studies of Hauser and Hauser (1939) at the University of Michigan, of Diehl *et al.* (1938–1940) and of Cowan and Diehl (1944) at the University of Minnesota, of Siegel *et al.* (1943) among the personnel of the Visiting Nurse Service of New York City, and of McGee *et al.* (1944) in a large industrial plant, in all of which there were adequate control groups, failed to demonstrate the practical value of "cold" vaccine whether of the orally or subcutaneously administered types, the Council on Pharmacy and Chemistry of the American Medical Association has still not accepted these vaccines.

Vitamins.—The controlled study of Cowan *et al.* (1942) yielded no indication that either large doses of vitamin C alone or large doses of vitamins A, B_1, B_{12}, C and D and nicotinic acid (niacin) have any important effect on the number or severity of infections of the upper respiratory tract when administered to young adults who presumably are already on a reasonably adequate diet.

Sulfonamides.—In the United States Navy during War II there was undertaken a program for the control of streptococcic infections and their disabling sequelae through the administration of prophylactic doses of sulfadiazine to about 250,000 naval trainees between December, 1943, and April, 1944, according to Carter (1945) the measure was later instituted at all naval training stations. Coburn (1944), in a preliminary report dealing with observations on only 30,000 men at three camps, stated that a continuous daily dose of 0.5 gm. of sulfadiazine (affording a mean level of 1.4 mg. per cent in the blood and perhaps 0.8 mg. per cent in secretion of the respiratory tract) was almost 85 per cent effective in preventing implantation of *Streptococcus haemolyticus*. The evidence which Coburn presented also showed that during the period of this trial there was a pronounced decline in the incidence

of catarrhal fever, which is the category in which the common cold is placed in the Navy Medical Service. It is difficult, however, to understand this decline since the sulfonamides are well known not to be effective against most viruses. One might presume that the ordinary common cold of virus origin did not figure in the study at all but that it included only such colds as were sufficiently complicated by bacterial infection to require dispensary or hospital attention; of course this is only armchair reasoning But I am sure that it is of the utmost importance to bring to the reader's attention the fact that this was practically a "closed" study in that the drug was administered to *all* personnel, since a comparable state of affairs could not obtain [illegible]

closed studies. Witness Siegel (1945) closely observed 128 physically normal feeble-minded children in an institution, half of whom were treated with sulfadiazine for periods of four to fifteen consecutive weeks and half left untreated Dosage ranged from 0.5 to 2 gm. daily (7½ to 30 grains); the average blood level of free sulfadiazine was 3.5 mg per hundred cc. on 1 gm daily dosage and 7 2 mg. on 2 gm daily dosage. In this study the incidence of acute infections of the respiratory tract was almost the same for the treated and for the control groups, though it was said that the treated patients recovered somewhat more promptly than the controls and experienced fewer complicated illnesses and fluctuations in severity.

Disinfection of the Air.—Suitably controlled experiments have now demonstrated the possibility of reducing the dissemination of respiratory diseases through disinfection of the air of enclosed occupied spaces. The means employ[illegible] the use of [illegible] col and prc[illegible] wholly within the province of architects, air conditioning specialists, etc. and not immediately to concern the practicing physician.

DENGUE

(Breakbone Fever)

Dengue is an acute infectious but not contagious disease that occurs endemically and sometimes epidemically in warm countries. Boylon, of Java, first described it in 1779, and the American, Benjamin Rush, in 1780 Graham, in Beyrouth, Syria, in 1903, first suggested that it is mosquito borne, and Bancroft in Australia, in 1906, whose work was confirmed and extended by Cleland, Bradley and McDonald in the same country in 1916, and by Siler, Hall and Hitchens in the Philippines in 1926, showed it to be transmitted by the yellow fever mosquito, *Aedes aegypti*; later work also convicted *A. albopictus* and *A. scutellaris hebrideus edwardsi*; *A. taeniorhynchus* is also suspect. Ashburn and Craig, in 1907, proved the dengue is caused by a filtrable virus; the patient is infective to the mosquito during six to eight hours before the onset of fever and the first two and a half or three days of the illness, and the mosquito, after an incubation period of eight to eleven days,

becomes and remains infective for life. In warmer regions where the climatic conditions favor the breeding of mosquitoes continuously dengue is usually endemic, but it may become epidemic in such regions upon the arrival of large numbers of susceptible individuals; this latter fact was emphasized unforgettably during War II when dengue posed a serious problem for us throughout vast regions of the Pacific area. There are some tropical regions, however, in which the disease occurs only in the form of explosive epidemics [illegible] veral years though both the mosquito vector and a sus- [illegible] sent; Simmons (1943), as well as many [illegible] ns a reservoir of the virus is main- [illegible] nkeys, in the inter-epidemic period. others, [illegible] tained in some lower anim[illegible] Dengue has several times been epidemic in the southern United States, the 1922 epidemic having assumed enormous proportions; Levy said that there were 500,000 cases in Texas between June and December. In the Greek epidemic of 1928, there developed 239,000 cases in Athens alone in one month.

There is considerable variability in the severity of the symptoms in outbreaks of dengue and perhaps also some geographic differences in the characteristics of the disease, which has given rise to the description of numerous "new" or "dengue-like" maladies (pretibial fever, Brushy Creek fever, Russian headache fever, shouten fever, etc.), but in the main the picture is that which follows. After an incubation period varying between three and thirteen days but with an average of about five days, the onset is sudden with severe headache, tenderness of the eyeballs and pain behind them, muscle and joint aches and usually excruciating backache (often much ag- [illegible]gravated by movement), extreme prostration, puffiness and redness about [illegible]e eyes, diffuse redness of the palpebral conjunctiva without lacrimation photophobia, rapid rise of temperature to 103° to 105° F. (39.5°—40.5° C.) [illegible]d a pulse rate which though moderately rapid during the first day soon [illegible]ecomes quite markedly slow despite the fever. On the third day the temperature usually falls rapidly and the patient feels much improved; however, [illegible]sually on the fourth or fifth day, the symptoms return and the fever is [illegible]requently higher in this second bout than it was in the first. Sometimes there are third or fourth bouts at intervals of a few days but in other instances the "saddle-back" type of temperature curve is not seen. The acute phase in most instances covers only a period of about seven days; recovery is usually by crisis, often with a sweat, diuresis and nosebleed. In the majority of instances—68 per cent in Cavanagh's (1943) series—there is a pea-sized enlargement and some tenderness of the lymph glands, the posterior cervical glands being the most commonly affected, with the anterior cervical, the epitrochlear, the axillary and the inguinal glands affected in the order named. An unusual phenomenon was observed in eighty-nine of the 318 patients of Kisner and Lisansky (1944) in that they exhibited a reversed diurnal variation of fever with a higher temperature from 8 A.M. to 2 P.M. than from 2 P.M. to 10 P.M. Two distinct types of rash are seen in dengue. Stewart's (1944) rash "A" is a toxic type which occurs on the third to fifth day and is variable in appearance and quite evanescent. Usually it is a scarlet diffuse redness of the chest and shoulders and upper arms with islands of normal skin half the size of a dime giving the appearance of white spots scattered over the scarlet background. This rash is suggestively measles-like in appearance and may also cause the observer to think of dermatitis medicamentosa in

the differential diagnosis. Rash "B" occurred in only about 20 per cent of Stewart's cases but it was seen in 86 per cent of Simmons' (1943) cases.

casionally in the roof of the mouth. In some cases the rash is blotchy and erythematous and the petechiae are absent, and sometimes there is itching The rash fades out in a few days One of the most constant features of the disease is leukopenia with a "shift to the left" in the granulocytes. Sometimes there is more albumin in the urine than would be expected from the febrile reaction. Weyrauch and Gass (1946) reported a few cases of orchitis and bloody seminal emissions as complications. Loss of appetite is complained of by practically all patients and in some there is nausea and vomiting and abdominal pain. Elek (1944) reported that altered taste was present as an important diagnostic symptom in 86 per cent of 154 patients studied in an endemic area in New Guinea. Almost invariable sequelae of dengue are anorexia, muscular weakness, insomnia, lack of ambition and mental depression, the latter lasting for several weeks Kaplan and Lindgren (1945) presented a series of neurologic case studies which bore, at least in the element of time, a direct relationship to dengue

Apparently the immunity of adult inhabitants of endemic localities results from previous infection, because when the disease is introduced into a new region practically all of the population are attacked and when individuals from dengue-free places move into endemic areas they contract dengue within such a short time that the disease is considered as an acclimatization fever. How long immunity lasts following an attack is not known but many clinicians in dengue regions believe that individuals not uncommonly experience repeated attacks within a few years; however, Simmons (1943), reviewing the evidence, felt that the immunity conferred by an attack probably lasts for a very long time. Nevertheless, McCarthy and Brent (1943) wrote of an area in East Africa in which many of the permanent inhabitants have mild attacks annually; Kisner and Lisansky (1944) described a case in which what

Dengue, like its kindred affection yellow fever, is capable of debilitating at a stroke large numbers of persons, but it is rarely fatal except through complications in aged and debilitated individuals and in pregnant women.

THERAPY

We have no specific therapy in dengue nor are symptomatic measures very helpful During the large experience of the disease in our Armed Forces in War II, the analgesic combination most frequently employed was 10

disease seemed to run a milder course; he found that the sulfonamides had no effect except occasionally to increase the nausea or anorexia. I have seen

no record of a trial of penicillin but would not expect it to be helpful. Hyman (1943) found that during convalescence the feeling of tiredness and general lassitude appeared to respond to various mixtures of belladonna and vitamins, at least sufficiently well to warrant a study of this type of therapy under favorable conditions Simmons (1943) said that convalescent serum has not been employed with success.

PROPHYLAXIS

It was shown during War II that the thorough screening of patients and the rigid application of measures designed to eradicate the mosquito vector are very powerful weapons against dengue even under the far from ideal conditions often prevailing in war time. The studies of Sabin and Schlesinger (1945), demonstrating the attenuating effect upon the virus of its serial passage through mice, indicated that virus so modified might be practicably employed as a vaccine. I have not seen a report of a large-scale controlled trial of this vaccine as yet.

DIPHTHERIA

Diphtheria is an acute infectious and contagious disease, caused by *Corynebacterium diphtheriae*, which is endemic in larger centers and often becomes epidemic during the winter months. It traditionally occurs chiefly in children but with the progression of immunization the age prevalence seems to have been shifted to older groups. For example, in an analysis of 108 cases reported in Wisconsin, Guilford (1946) found that thirty-five were in persons beyond twenty years of age. Diphtheria is much less often food-borne (milk or milk products) than is scarlet fever. The incubation period is two to five days. In the beginning of the attack the patient is but moderately indisposed, having a little soreness of the throat and slight elevation of temperature. However, the typical membrane soon begins to form in the throat and by the third or fourth day is quite thick and may cover a considerable part of the fauces Absorption of toxins from the local lesion gives rise to profound constitutional symptoms, and there may be definite degeneration of the heart muscle, kidneys and peripheral nerves. Bronchopneumonia is a complication in nearly all the fatal cases.

Average cases, if properly treated with antitoxin, show a rapid subsidence of severe symptoms and are fully convalescent in seven to ten days. In especially virulent cases, or those not properly treated, the symptoms may gradually increase in intensity to about the sixth day, when there will be considerable obstruction to the nose and throat by the spreading membrane, a massive cervical adenitis and cellulitis ("bull-neck"), rapid and feeble pulse, and perhaps subnormal temperature. Then coma supervenes upon the profound sepsis and finally death. In that type of the disease in which the membrane first appears in the posterior part of the nasal cavity, and in the laryngeal type where the symptoms are respiratory from the beginning, the prognosis is especially poor. The chief laboratory aid to diagnosis is still the growing of the organisms from the throat in Loeffler's medium, either upon the slant overnight or upon the swab in the physician's pocket in a shorter period of time, but Goldie and Maddock (1943) stated that the use of a tellurite medium simplifies the isolation of the organism from milk.

According to the Babylonian Talmud (352-427 A.D.), the ancient Hebrews so much feared diphtheria that upon the discovery of the first case in a community the *shofar* was blown (for all other contagious diseases it was sounded only after the third case was reported). The classical description was that of Aretaeus the Cappadocian (*circa* 100 A.D.). Aëtius, in the sixth century, mentions paralysis of the palate as a sequel. A number of epidemics of the [illegible]

first recorded cases in America occurred in Massachusetts in 1659. To me it seems a strange thing that the diminished liability to the disease after adolescence was apparently not mentioned in the literature before the publication of Heberden's famous *Commentaries* in 1802 Bretonneau gave the disease its present name in 1826, but the laryngeal and pharyngeal types were not recognized as being the same malady until 1880 In 1883-84, Klebs and Loeffler identified and proved the causal relation of the organism. Von Behring developed antitoxin from the laboratory side and Roux from the practical in 1894; the former worker introduced toxin-antitoxin immunization in 1913, and Schick introduced his test in that year also The present pandemic developed in the middle of the last century and has reached all parts of the world, though it is unquestionably much more severe and probably more prevalent in colder climates, especially the north temperate zone, than in the tropics, however, during War II cutaneous diphtheria occurred in troops in the Pacific area, Burma, and the Mediterranean and there were frequently some pharyngeal cases associated with these outbreaks. Since 1941 there has been an increase in Northern Central Europe in both the incidence and severity of diphtheria; indeed, according to Stuart (1945), diphtheria proved to be the leading epidemic war disease on the Continent and it remains high on the list of postwar problems in Germany and the liberated countries. So great has become the risk to American soldiers in occupation that only immune individuals are now being sent to that theater as replacements and dependents under the age of thirty-five years have been immunized prior to their departure for Europe. It has now become possible to effect a definite correlation between the severity of the disease and the type (*gravis*, *mitis*, and *intermedius*) of infecting organism. Cases of the most malignant type have occurred only sporadically in the Western Hemisphere, though Wheeler and Morton (1942) pointed out that the epidemic in Halifax was of that type and that the disease had probably been brought to the port by the crew of a Norwegian tanker. Fleming (1944) expressed the opinion that the introduction of the virulent strains would be very heavy when our service men and women returned from Europe at the end of War II, this prediction has not been borne out in the main, though an outbreak of unusual severity occurred in Baltimore in 1944, and Frobisher (1946) established that these cases were caused by a distinct colony variant designated as the *minimus* type. Throughout the world as a whole mortality has considerably diminished, however, and it is but a question of time until the newer immunization methods will effect a similar reduction in the world morbidity figures. In the United States, in 1945, in ninety-three representative cities with a total population of 38,060,662, there were only 321 deaths from diphtheria, and in thirty-seven of these cities there were no deaths at all

employed. Wesselhoeft (1940) said that hot glucose irrigation of the throat every three hours greatly reduces the foul odor in a diphtheria ward; if done gently it is apparently very soothing Many men like to use a steamy inhalant (see Common Cold) for its soothing effect on the mucosa; perhaps it is best here to omit drugs and use just the steam alone. The expectorant action of syrup of ipecac may aid in loosening the membrane in severe cases; 10 minims to 1 drachm (0 6–4 cc.), depending upon age, every three hours.

In a report from the Medical Consultants Division of the Surgeon General's Office (1945), the application of sterile warm saline compresses to the cutaneous lesions was recommended and it was further said that compresses soaked in penicillin solution (250–500 units per cc.) give a quicker effect. Applications of ointments, dyes and sulfonamides were declared to be of no value and possibly harmful.

Diet.—If vomiting has supervened, all mouth feeding must cease and sole reliance be placed upon the intravenous administration of dextrose; if much fluid is being lost dissolve the dextrose in Locke's solution instead of water to make up the loss in salts. Many young children refuse all food in the severe cases even if not vomiting; if possible they should be got to take some milk, which may be fortified with cream; or it may be offered in the form of eggnog which is very nourishing. The following eggnog contains no mixture of liquors and only one fourth as much alcohol as the familiar beverage: to the well-beaten yolk of an egg add the following with stirring—½ pint milk, 6 teaspoonfuls brandy and 5 level teaspoonfuls sugar. This should be offered for a few sips at frequent intervals during several hours. The addition of a small amount of nutmeg is pleasing to adults but not always to children; the white of the egg, beaten with a little sugar and placed on top, makes the whole more appealing especially if dusted with nutmeg.

As soon as possible the patient should be placed upon such a diet as that described in Common Cold.

Quarantine and the Carrier.—The patient should be kept isolated until two successive nose and throat cultures are negative, which happens within two weeks after recovery in most instances. Attempts to shorten this period through the use of the older type of antiseptic spray, gargle or swab, or the snuffing of sulfonamide powders, have yielded disappointing results, but the local use of penicillin has met with qualified success. Berman and Spitz (1945) found their ten carriers becoming negative in five days when treated with local applications of 500 units per cc. to the nose and throat, whereas seven of their twelve controls required five weeks to become negative and the other five only became negative when they were treated with penicillin after two more weeks. Kocher and Siemsen (1946) were successful in the treatment of twenty-three out of thirty-one cases with lozenges containing 500 to 1000 units plus a nasal spray of 1000 units per cc.; tonsillectomy was helpful in clearing the remaining cases But Stern and Grynkewich (1946) obtained inconclusive results with the use of a spray, and Paull *et al.* (1946) failed with aerosolized penicillin But parenterally administered penicillin has yielded better results, Weinstein (1947) and Karelitz *et al.* (1947) reported marked reduction in the duration of both the convalescent and carrier states, the former advocating the use of a minimum of 240,000 units per day for twelve days.

Paralysis.—The various types of paralysis associated with diphtheria are seen in from 10 to 25 per cent of cases. Involvement of the swallowing muscles

which sometimes occurs at the height of a severe case requires nasal or pa-

and nearly always fatal.

that of the arms or legs,
comes on in from one to six or seven weeks and is usually transient. Recovery may be hastened by massage, and some men also feel that the use of strychnine sulfate in tonic doses is justified. As this condition sometimes precedes late cardiac failure the patient should be kept perfectly quiet. Of course antitoxin "big and early" will prevent these paralyses; in those appearing after convalescence is established it is not indicated.

Emergency Relief in Laryngeal Cases.—The dyspnea is caused by one or more of the following: a partially detached membrane that has been drawn down into the lumen of the glottis, obstruction by tenacious mucopurulent secretion; edema of the inflamed subglottic tissues; spasm of the glottis. The measures available for the relief of this very serious condition—removal of membrane with forceps or with an applicator introduced through the laryngoscope, intubation, tracheotomy, aspiration—will not be described here as they are all highly specialized procedures that can only be learned upon the cadaver and in the ward and not from the pages of a book.

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Who Should Be Immunized and When.—In the period 1914–1923, Schick compiled statistics indicating that 86 per cent of adults in large cities were immune to diphtheria, which meant, since immunity is transmitted through the placenta, that the same proportion of infants was born immune in that era. The studies of others having established the duration of this neonatal immunity as six to nine months, it became customary to assume that infants were safe during the first half or three-fourths of their first year and that diphtheria immunization was most profitably performed toward the close of that year In the main this is still the custom, but since studies in recent years have indicated that from 50 to 60 per cent of young adults in the United States, Canada, England and Australia are not immune to diphtheria, there are some observers who are now urging that immunization take place earlier than has been customary. Of course the reason for the decline in immunity among adults is the present-day lack of contact with diphtheria bacilli since so many individuals have been immunized and the incidence of the disease, at least in the countries above listed, has greatly declined, for the persistence of artificial immunity depends upon a critical degree of exposure. It would seem not unlikely that we are going to see a considerable increase in the incidence of diphtheria in adults in the years to come unless our immunization programs encompass older children as well as infants.

Despite the fact that the assumption of protection to the newborn infant as a result of the mother's immunity is nowadays no longer felt to be valid, diphtheria is not a frequently occurring disease during the first year of life. Nevertheless a few clinical investigators have sought to

stein (1935) have shown that routine immunization of all infants under six months will often fail because of the inability to graft an active immunity upon a pre-existing passive one in the case of those infants who have re-

ceived immune protection from their mothers. Accordingly the most accurate gauge of immunity in the baby is the reaction to the Schick test performed upon the mother Leibling and Schmitz (1943) found that a Schick test performed upon the pregnant woman would not only separate the negative from the positive reactors but would at the same time serve as a secondary stimulus to the already Schick-negative mother, thus resulting in an increased placental transfer of passive immune bodies to the offspring; they also determined in a small number of cases that active immunization of the *non-immune pregnant mother* provides a prolonged protection of the infant during the period of least resistance. Cohen and Scadron (1946), in immunizing the mother against both diphtheria and pertussis, proceeded as follows: (a) *intradermal test with 1:10 dilution of diphtheria toxoid* was used on all Schick-positive cases (Moloney test); (b) if the reaction was very marked within one-half hour, fluid diphtheria toxoid was omitted and plain *pertussis vaccine given, or the initial dose of 0.1 cc. of diphtheria toxoid* was followed by 0.25 cc., 0.5 cc. and 1 cc. added to the pertussis vaccine in the same syringe. They were able definitely to state that active maternal immunization had *no observable deleterious effects upon the offspring or* ill effects upon the pregnancy, though the mother at times had a local and less often a systemic reaction.

Alum-Precipitated Toxoid.—This preparation is injected subcutaneously at the deltoid insertion in a dose of 0.5 or 1 cc., depending upon which manufacturer's product is being used. According to Stebbins (1943), the Diphtheria Sub-Committee of the Committee on Administrative Practice of the American Public Health Association recommends that two doses should be given children under school age, with an interval of one month between. In his authoritative review, Edsall (1946), of the Massachusetts Department of Public Health, also emphasized the lack of justification for attempting immunization with one dose. Being an insoluble substance this preparation raises a firm nodule at the site of injection and around it there appears and persists for a few days a trifling inflammatory reaction, the nodule becoming smaller as the material is absorbed and disappearing completely in six weeks. Very rarely—practically never in children under two years of age—there may be more marked local redness and swelling and discomfort and sometimes malaise, anorexia, aching and a slight fever. But these reactions occur so seldom up to six or eight years of age that the possibility is usually disregarded as being of no moment except in individuals known to be *definitely* allergic. Occasionally there occurs a sterile abscess at the site of injection, dc [illegible] body; but this is a [illegible]

[illegible] d subcutaneously in a dose of 1 cc. According to Stebbins (1943), the Diphtheria Sub-Committee *of the Committee on Administrative* Practice of the American Public Health Association recommends that for children under school age three doses be given at intervals of one month. Edsall (1946), in his review above referred to, also stated that two doses is not enough. General reactions are rare in children under eight years of age and in this group local reactions of any moment occur very infrequently, but in older children and adults the incidence of both types considerably increases. An *intracutaneous test* dose of 0.1 cc. of toxoid diluted with salt solution (1 in 20) is *sometimes* given and the toxoid then withheld from those who show a positive skin

reaction (a flush of 10 mm or more in diameter, with perhaps some slight swelling, after forty-eight hours—Moloney test); such skin-test solutions are distributed with some of the commercial preparations. In the immunization of military and civilian personnel in or preparing to enter the European theater of occupation in the post-War II period, the fluid toxoid is started with a 0.1 cc. subcutaneous injection as a test dose followed in forty-eight hours by 0.5 cc. subcutaneously, this followed in three weeks by 1 cc, with a final 1 cc. subcutaneous injection after an additional three-week interval; this method allows for the elimination of severe reactors at any point in the series.

Choice of Preparation.—It is my impression that for mass immunization

rations containing alum-precipitated toxoid combined either with tetanus toxoid or with both tetanus toxoid and pertussis vaccine (see the article on Tetanus).

Rapidity of Immunization.—It is now considered that with either the fluid toxoid or alum-precipitated toxoid methods antitoxin begins to appear in the blood in a few days and full immunity is reached in 95 per cent or more children in four to six weeks However, Grant (1946) found that where *gravis* strains of diphtheria bacilli are prevalent the degree of protection is not so great as we are accustomed to obtaining, though mortality is practically eliminated.

Retesting.—Ideally all individuals should be Schick tested three to six months after immunization; the positives can then be reimmunized with reasonable assurance of success by either method. Preliminary desensitization had perhaps best precede the second trial Fischer *et al.* (1940) pointed out that children tested during the febrile period of an acute infectious disease in whom bullous Schick reactions develop should be retested some time after recovery before being considered susceptible to diphtheria.

Duration of Immunity.—A number of men are now urging that upon en-

now held necessary for such protection being much more than the minimum content (1/250) to insure Schick negativity in most instances And even Schick negativity is not retained by all children to school age; Schwartz and Janney (1938), retesting 145 children six or seven years after immunizing them with three doses of fluid toxoid, found that 22 per cent had reverted to a Schick positive test. Benjamin *et al* (1940) found 14 9 per cent of their larger series positive after five to eleven years, which was twice the proportion positive after four to five years. Duke and Stott (1943), in a rural area in England in which 95 per cent of the children had been immunized, found the proportion who had lost their immunity rose steadily from 4 per cent after two years to 18 per cent after six years. In London, Freeman (1942) found over four-fifths of 2425 children at school entry age Schick-positive. It is a frequent practice here in the United States nowadays to give a small dose of 0.1 to 0.2 cc of toxoid to reinforce the declining immunity about three years after the primary immunization. Vollmer and Wegman (1945) found that the percutaneous method was not satisfactory for this

purpose. Bousfield (1945) is experimenting very interestingly with a t pastille which may be given by mouth for this "booster" dose.

Tonsillectomy and Immunity.—Buice's (1934) study seemed convinc to show that tonsillectomy neither decreases the incidence of diphtl nor increases Schick negative immunity; nevertheless, Eller and Frobi (1945) found that in an outbreak of very severe diphtheria in Baltim almost all of the cases occurred in children who had not had their ton removed.

Prophylaxis with Antitoxin in Nonimmune Exposed Cases.—Formerly was the routine practice to give an immunizing dose of antitoxin to childre who had been exposed to diphtheria and who had not been immunized. Nowadays, it is more customary to wait a while, watching the child carefully for the early signs of the disease and then giving a suitable therapeutic dose of antitoxin should they appear. This change of policy has followed the repeated observation that even a small dose of the serum may cause an alarming reaction or render the patient sensitive to a therapeutic dose subsequently administered. Of course if the child cannot be watched, he should be given 1000 units of ordinary treatment antitoxin as soon as possible; this establishes an immediate passive immunity which lasts for about three weeks.

Combined Methods of Immunization.—See article on Tetanus.

DYSENTERY

Nearly all the notable writers since that able Byzantine compiler, Alexander of Tralles (525–605 A.D.), have left accounts of dysentery. During the Thirty Years' War in the seventeenth century it ravaged the Continent and England, where the great Sydenham among others described it. The disease continued widely prevalent throughout the eighteenth century in Europe, and following Clive's victorious campaigns the varieties encountered by British medical officers in India began to be described. The etiologic agents of bacillary dysentery were discovered by the following workers: Shiga in Japan (1898), Kruse in Germany (1900), Flexner in America (1900), Strong and Musgrave in the Philippines (1900), and the Y-bacillus by Hiss and Russell in America (1903). Lambl probably saw the causative ameba of the protozoan type of the disease in 1860 when he discovered *Giardia intestinalis*, but the definite differentiation between epidemic bacillary dysentery and endemic amebic dysentery was made by Koch (1883) and Kartulis (1886–1891) in Egypt. The recognition of *Isospora hominis* infections in man occurred during War I; perhaps I am a bit hasty in recognizing as *virus* dysentery the entity more often referred to as epidemic vomiting and diarrhea, acute infectious gastroenteritis or "intestinal flu."

The various types of "dysentery" will be found in alphabetical order among the Infectious Diseases under the following titles. Amebiasis, Balantidiasis, Coccidiosis, Epidemic Diarrhea of the Newborn, Giardiasis, Infantile Diarrhea and Vomiting, Shigellosis, and Virus Dysentery.

EPIDEMIC DIARRHEA OF THE NEWBORN

In recent years a number of epidemics of severe intestinal intoxication occurring as localized outbreaks among a hospital's population of newborn infants have been reported from several cities in the United States, Canada and England Both sexes and all races are attacked but only during the first two or three weeks of life, older children and adults being apparently immune. The chief symptoms are the passage of numerous watery yellow stools without blood, mucus, or pus, great distention, occasional vomiting, marked dehydration, great and precipitous weight loss, possibly but not invariably fever, drowsiness, shock and a very high mortality The disease is extremely contagious but the etiologic agent has not yet been determined, though the study of Buddingh and Dodd (1944) pointed strongly toward a virus in the causat role. In an outbreak in one of the Milwaukee hospitals (Cron, Shutter a Lahmann, 1940) breast-fed infants either did not contract the disease or they did so were able to survive the attack; this has also been the experienc elsewhere In our epidemic acute enteritis was found in 87 per cent of the sixteen babies autopsied, with pneumonia the next most frequent finding, though the latter predominated over all other findings in only three instances, in several instances there was aspiration pneumonia and in two of these it seemed to be the cause of death as there was no evidence of enteritis in these cases. However, in other epidemics elsewhere enteritis has not been always a predominating finding, Sakula (1943) reported findings suggesting an acute toxic condition rather than an intestinal infection, the liver, thymus and suprarenals being notably affected

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These epidemics do not respond typically to the measures employed in bacillary dysentery and ordinary infantile diarrhea. There are reports in which it seems that the sulfonamides have been of some value, but High *et al* (1946) found that neither the absorbable nor the non-absorbable members of the series prevented the development or altered the course of the disease penicillin also failed to be effective, both in this series and in that of Allez *et al.* (1946). High *et al* also failed to find gamma globulin effective either as a therapeutic or prophylactic agent Transfusions from donors given a sulfonamide twenty-four hours previously, convalescent serum, autogenous vaccines, all failed in the Milwaukee epidemic. It was thought that breast milk, begun as soon as possible after a supply was obtained, was helpful, but the only babies who either escaped or survived the epidemic were those nursed upon human milk from the time of their birth Mayes (1947) felt that in an epidemic the inoculation of the large intestine or rectum of infants not being breast fed might be indicated Lyon and Folsom (1941), in an epidemic in Huntington, West Virginia, felt that citrated whole blood (30 cc. injected into the gluteal region) from a patient recently convalescent from clinical influenza was astonishingly helpful in three of their cases, and they suggested the possibility that epidemic diarrhea of this type may be an expression of infection with influenza virus in the newborn. Anderson and Nelson (1944) felt that the most marked improvement in the infants involved in their epidemic resulted from the raising of a low carbon dioxide combining power of the blood to the normal range by the parenteral administration of alkalis. It seems to be the consensus that to safeguard against outbreaks of this

dreadful malady some means must be found for increasing the already prodigious efforts to attain asepsis in the maternity and newborn quarters of modern hospitals. The Milwaukee group is making a strenuous effort to increase the incidence of breast feeding as a precautionary measure of apparently proved value.

EPIDEMIC ENCEPHALITIS

(Encephalitis Lethargica, St Louis Encephalitis, Japanese Type B Encephalitis, Australian X Disease, Equine Encephalomyelitis, Russian Encephalitis, Sporadic Encephalitis of Unknown Origin, Other Virus Diseases of the Nervous System)

Encephalitis lethargica first appeared as an apparently new disease on the Continent in 1915 and for a few years thereafter was epidemic throughout the western world Many investigators now believe this outbreak to have been identical with the "nona" of the 1890's and indeed many earlier visitations, the earliest of which perhaps was that described by Sydenham as having prevailed in London in 1673 to 1675 Since 1926 only an occasional sporadic case has been seen It was thought that this encephalitis of von Economo caused by a filtrable virus, perhaps related to but not identical with those of herpes and influenza, but this fact was never established The acute clinical manifestations were very complex and appeared either suddenly (often after a period of enforced activity) or gradually; often, but by no means invariably, there were the following symptoms: increasing drowsiness, slight fever, diplopia or other eye muscle disturbances, salivation and head cold. After the patient took to bed he usually lay relaxed and absolutely quiet, with one or both lids ptosed, apparently but not actually asleep; indeed, insomnia was of frequent occurrence despite the mask of deep stupor. Other patients manifested evidences of motor irritation from the beginning—movements of the pill-rolling, Parkinson type—or they were choreoid, or clonic-spasmodic. Mentality was usually impaired, especially as to memory, attention and orientation. Emotional disturbances were common, and in some cases marked alterations of character and oddities of behavior were outstanding features. Delirium sometimes alternated with periods of stupor. In many cases there was an increase in globulin and sugar and a slight increase in the cell count in the spinal fluid. The disease occurred in the winter and spring and affected principally individuals in the third and fourth decades; the mortality was between 25 and 40 per cent. Convalescence was very slow, and the sequelae, from which recovery was also very slow if it occurred at all, were much dreaded; persistent insomnia or prolonged somnolence; Parkinson-like syndromes; autonomic pupillary, respiratory, cardiac, sphincter, etc., disturbances; mental impairment; psychoneurotic manifestations, and so on.

The newer types of encephalitis differ markedly from the above. St. Louis encephalitis appeared in several counties in Missouri in 1933 and recurred in that area in 1937. In the first epidemic there were 1097 cases with a mortality of about 20 per cent, the second time the mortality was 24.8 per cent with only 431 cases, most of the deaths in both epidemics occurring in elderly people. A few other outbreaks of rather smaller proportions have since occurred in that and in other areas of the United States. St. Louis encephalitis occurs only in the late summer and early fall and affects individuals of all ages but principally those in the upper age groups. The attack usually begins

with chilliness and malaise, vomiting and often severe abdominal pain, sometimes quite high fever and often a disproportionately slow pulse, grippe-like aches and pains, and early signs of cerebral involvement, such as severe headache and stiff neck, mental confusion and perhaps even delirium, convulsions or coma, tremors and a variegated lot of other neurological signs; but notably absent or at most only transiently present are the ocular manifestations characteristic of encephalitis lethargica. Globulin, pressure and the cell count (predominantly lymphocytes) are usually moderately increased in the spinal fluid but the sugar remains normal in most instances. The course may be very stormy but recovery is usually complete in two or three weeks and mild subjective nervous complaints are the most common residuals (as revealed in the Bredeck *et al*, 1938, follow-up study of the first epidemic in St. Louis). It is believed that many subclinical cases occur during an epidemic.

A number of quite similar outbreaks have been reported from Japan and nearby areas, a mortality of approximately 20 per cent being reported from Okinawa by Lewis *et al.* (1947). A filtrable virus has been recovered in both St. Louis and Japanese B encephalitis, has been cultured and established in several experimental animals, but it appears that the two viruses are distinct or at least distinctive strains of the same virus. Apparently St. Louis encephalitis occurs only in the United States and Japanese B encephalitis only in the Japanese area, though it seems probable that the latter or a very closely related virus was also involved in the epidemics in Australia in 1917 and 1925 of the encephalitis known as Australian X disease; probably, too, Russian autumn encephalitis is identical with the Japanese B variety. In far eastern Russia a disease similar to Japanese B encephalitis attacks principally adult males who work in the deep forests in spring and summer, but Casals and Webster (1944), of the Rockefeller Institute, compared this virus with several others of the encephalitis group and found it unrelated to all except that of louping ill, a disease of sheep, which it is said to resemble closely; indeed, the Russian workers, Silber and Shubladze (1945), confirmed these findings but reported that a very similar encephalitis has since appeared in European USSR with an immunologically dissimilar etiologic virus.

Equine encephalomyelitis is a very recently recognized disease in man though it has been known in horses for a long time. The first outbreak in the human was reported in 1938, first from the New England and then from the Western States. I believe that the largest epidemic to date was that in and around North Dakota in 1941, in which there were about 3000 cases with 200 deaths. The disease occurs in summer and is clinically very similar to St. Louis encephalitis except that it is usually abrupt in its onset and sharp and short in its course, and such permanent residuals as paralyses and mental changes are common. Equine encephalomyelitis has been shown to be due to a filtrable virus recoverable from both horses and man but the eastern and western strains are different; there is also a distinctive Venezuelan strain which is known also to have made its way over to the island of Trinidad, but most of the human infections with this strain have been acquired in the laboratory. It has been reported (J A M.A., March 11, 1944) that the encephalomyelitis of Brazil is not caused by the Venezuelan strain but by the eastern strain of our North American type of the disease. The work of several investigators strongly indicates that St. Louis encephalitis, Japanese B encephalitis, and the western and eastern types of equine encephalomyelitis are primarily diseases of birds, the common barnyard fowl as well as wild birds, which have

become well adapted to the virus and are very little disturbed by the infection. It would appear that the infection of man, or the horse and other mammals, by infected mosquitoes is merely an accidental and not a natural part of the cycle, but the mammals manifest severe symptoms because they are not yet well adapted to these viruses. So far, I believe, nine species of mosquito have been convicted as vectors of animal infection but as yet no human case has been proved to have been caused by the bite of one of these insects; nevertheless, these infections have been authoritatively grouped together under the term "arthropod-borne virus encephalitides." Since throughout the period of the occupation of Japan many civilian and military personnel will be returning from that area to this country, it is of interest to note that Reeves and Hammon (1946) found Japanese B virus susceptible of laboratory transmission by North American mosquitoes. Russian spring-summer encephalitis is conveyed by the woodtick, and St. Louis encephalitis can be conveyed experimentally by the common dog tick and the common chick mite; but it is felt that while these insects, feeding on birds and mammals, may play an important role in establishing and maintaining a reservoir of infection in these animals, the disease is probably conveyed to human beings only through the bite of the infected mosquito. Japanese B, western equine, Russian spring-summer, lymphocytic choriomeningitis (see below) and St. Louis viruses have all been isolated from the blood, but no instance of the direct insect transmission of the disease from man to man or indeed from lower animal to man has as yet been recorded.

To complete the list of types of epidemic infectious encephalitis, it should be mentioned that sporadic cases of encephalitis are being reported that do not, immunologically at least, fit into the description of any of the above-listed entities. Lymphocytic choriomeningitis, which is not precisely an encephalitis, is characterized by sudden onset with fever, headache and meningeal signs and cell counts in the spinal fluid higher than those in other virus diseases of [illegible] system with the exception of mumps meningo-encephal[illegible] uenza and the prognosis is [illegible] hree weeks; Dalldorf *et al.* (1946) found the incidence of choriomeningitis virus carriage in house mice in Greater New York to be approximately 4 per cent. Toxoplasmic encephalitis is described elsewhere in the book (see Toxoplasmosis).

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There are no specific remedial agents and only symptomatic treatment is available. During the acute stage, light but ample feeding, the forcing of fluids, the keeping of the body clean and the protection of the patient from all annoying sensory stimuli, and in some instances the use of salicylates to relieve pain, are indicated. In the treatment of the insomnia or the excited states, of course, resort must be had to full doses of sedatives (see Insomnia), but it is possibly advisable in choosing among the barbiturates to omit phenobarbital, for the Ziskinds (1937) found that this drug aggravates rigidity in established parkinsonism. During the first St. Louis epidemic (Eschenbrenner, 1934) patients admitted to the Isolation Hospital were given spinal puncture on admission and it was repeated when there recurred evidences of increased pressure or meningeal irritation (Slesinger, 1936, in the Windber, Pennsylvania, outbreak, found the routine initial puncture of no advantage). Ten per cent dextrose solution was routinely given intravenously, daily during

the severe stage, 750 cc. to adults and correspondingly smaller doses to children. Those with severe signs of cerebral edema were given 60 cc. of 50 per cent dextrose solution intravenously every twelve to twenty-four hours, efficaciously in most cases. Gareau (1941) used this treatment frequently also in his cases of the equine type. Drastic saline purges were used in some instances in the effort to reduce the edema further. Retention of urine in the women and older men sometimes required several catheterizations or the use of the retention catheter for several days. Hyperpyrexia, frequent in the acute cases yielded to tepid baths, alcohol rubs and the ice-bag to the head. Delirium tremens responded to large doses of paraldehyde.

The sulfonamides have been tried in numerous instances and have always failed; however, Meiklejohn and Hammon (1942) thought that judgment should still be reserved since in an outbreak of St. Louis encephalitis in which they used sulfadiazine they did not have the mortality which they felt might have been expected. Most men see no reason to expect anything from convalescent serum, but Slesinger felt that it was of some value in the twenty-two cases of the St. Louis type in which he tried it. Nicholson (1945) used ooled plasma to combat brain edema in one case of encephalitis lethargica nd thought that the results were good. It may be worthwhile recording that ulkin *et al* (1946) reported that ether anesthesia considerably reduced the ortality rate in certain of the experimental neurotropic virus infections.

In the more stuporous patients nasal tube feeding must be resorted to. borka's formula (P, 70, C, 195, F, 160, Cal., 2500, fluid, 1760 cc.) follows:

Mix together and boil
1000 cc milk
3 eggs
120 gm sugar or lactose
300 cc cream
3 egg whites

Cool and add the following
100 cc. orange juice
3 teaspoonfuls brewers' yeast
15 cc. cod liver oil

Strain through a very fine sieve Serve at body temperature, 150 to 200 cc every two hours.

The treatment of the psychoneurotic sequelae, which characterize mo notably encephalitis of the lethargic type, being largely systematic attempt at rehabilitation, cannot be described here Arsenic, iodides, and indeed practically all the other specifics and near-specifics have been tried as aids to this process, and found wanting To control parkinsonism (muscular rigidity and poverty of movement, tremor, drooling, upward rolling of the eyes and eye-closure), drugs of the belladonna series are used. The alleged therapeutic value of acriflavine, trypan blue, pyridoxine, and fever therapy has not been confirmed Hall (1943) cited the case of a woman who had difficulty in chewing and swallowing her food except at about two o'clock in the morning, and pointed out that this relief of inhibition, or whatever it may be, during the night hours or when half-awake is not uncommon in the automatic acts such as speech and gait. He also pointed out that in cases of disturbance in gait self-confidence is often restored by taking lightly hold of somebody's arm or by the use of some type of brace for its psychical effect. Hall said that in his experience least effect from the belladonna drugs is obtained in attempts to control the eye symptoms, which is unfortunate because sometimes they are the only disability preventing employment. In some of his worst cases of drooling which had not been checked by the belladonna drugs he succeeded

with deep x-ray therapy over the salivary glands. It seems to me that surgical attempts to interrupt nervous pathways are still in the early experimental stage since there does not seem to be as yet agreement between neurologists, neurophysiologists and neurosurgeons as to the exact connecting links between the muscles and the brain at which interruption might most suitably be attempted.

The belladonna drugs are used as follows:

(*a*) Atropine sulfate is started at 1/80 grain (0.75 mg.) thrice daily and increased by 1/120 grain (0.5 mg.) twice daily until maximal therapeutic effects, or toxic disturbances, are obtained In some instances doses of ⅙ to ⅓ grain (10–20 mg.) daily are given for many months; this was the average optimal, indeed, in Hall's (1937) series, and in one of his cases 54 mg. was required and tolerated. Jewett *et al.* (1938) also used high dosage satisfactorily. Schlezinger and Alpers (1941) used a synthetic atropine-like drug, syntropan, and thought it of definite value; maximum benefit was experienced when the total daily dosage of 2.4 gm. could be tolerated.

(*b*) Bulgarian belladonna: for some years there has been an impression on the Continent that a white wine decoction of Bulgarian belladonna was superior for this purpose to atropine. In England, the findings of Hill (1938) and of Alcock and Carmichael (1938) were conflicting. In the United States, Neal and Dillenberg (1940), making trial of the decoction under the auspices of the Matheson Commission for Encephalitis Research in New York City, obtained results in approximately 100 patients which they described as far superior to those obtained with any other form of symptomatic treatment. The decoction having been found to deteriorate upon standing, a tablet has been prepared and is available under the name "bellabulgara." It was found necessary to use sufficient dosage (which must be separately determined in each patient) to cause marked dryness of the throat and blurring of vision and then, when these symptoms subsided after a few days on this dose, to push up to the point of causing really toxic symptoms, such as gastro-intestinal and urinary disturbances, headache and dizziness. Fabing and Zeligs (1941) found a white wine extract of U.S.P. belladonna root fully as effective as the Bulgarian preparation; the point seems to be that white wine extracts yield products qualitatively different from those obtained by hydroalcoholic extraction (tinctures)—*if* they do, I think some time must pass before we can be sure of this.

(*c*) Scopolamine hydrobromide (hyoscine), 1/200 to 1/100 grain (0.3–0.6 mg.) several times daily.

(*d*) Stramonium: the powdered leaves (in capsules or pills) are given at one- or two-hour intervals until good effect is obtained, after which a maintenance dose is employed. In the beginning 15 to 30 grains (1–2 gm.) may be distributed during the twenty-four hours; a maintenance dose of 8 grains (0.5 gm.) has been found to be well tolerated for many months. Of the tincture, 60 to 90 minims (4–6 cc.) three times daily is generally effective.

(*e*) Combined alkaloids: an alkaloid mixture consisting of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide was reported by Vollmer (1942) to be more effective than the other agents.

Hurst (1934) found that he could continue the use of a drug of the above group in some patients after there was complaint of dryness of the mouth and paralysis of accommodation by combining with it 1/10 grain (6 mg.) pilocarpine nitrate; some of his patients received doses as large as 2/5 grain (24

mg.). Solomon *et al.* (1937) found benzedrine sulfate (amphetamine) of some adjuvant value, especially when symptoms of drowsiness and lack of energy predominate; Finkelman and Shapiro (1937), Matthews (1938), and Davis and Stewart (1938) had similar experiences

PROPHYLAXIS

A bivalent vaccine against equine encephalomyelitis of both the eastern and western types has been extensively employed in horses and mules, it is said (Bulletin of the U.S. Army Medical Department, March 1944) that since inauguration of the annual vaccination of all horses and mules in the U S Army in 1939 only one case had occurred and that in an animal that came down with the eastern type after having been immunized only against the western type. These vaccines are now commercially available for human use and it is thought that they will probably be very effective in man. However, since both morbidity and mortality have been low in most outbreaks of the disease in the human, Hammon (1943) said that mass immunization programs with this vaccine are not indicated, though he felt that the agent should be used in selected groups of heavily exposed persons. Vaccines against the St. Louis and Japanese B viruses have also been developed, and Sabin (1947) reported the vaccination of over 300,000 persons with the latter on Okinawa during the summer of 1946; no instances of demyelinating encephalopathy resulted from these vaccinations, but it seems that the special conditions prevailing on the island did not permit a true evaluation of the protective value of the vaccine. The Russians seem to have developed a fairly satisfactory vaccine against their spring-summer tick-borne encephalitis; Smorodintsev (1944) reported that only two out of 925 vaccinated personnel came down with the disease whereas twenty-seven were afflicted with it among 1185 unvaccinated controls

EPIDEMIC PLEURODYNIA

(*Devil's Grip, Epidemic Myalgia, Bornholm Disease, Bamle Disease*)

Epidemic pleurodynia is an acute infectious disease characterized by sudden onset with excruciating muscular pain at the site of the attachment of the diaphragm to the anterior thoracic wall on either side, in the epigastrium and sometimes in the shoulder girdle and neck as well, marked increase in rate and decrease in amplitude of respirations, sometimes several degrees of fever with or without nausea and vomiting, and rather constant headache. The aching muscles are often tender and sometimes noticeably swollen. The pain usually leaves within twenty-four hours as suddenly as it came; the fever also subsides, the patient breaks out into a sweat and, being greatly relieved, falls into a refreshing sleep There is often an attack of lessened severity one or two days to a week later, but a third seizure is rare. In an epidemic in Brooklyn, New York, involving 171 cases, Howard *et al.* (1943) reported that five of the adults had manifested apathy and photophobia and experienced vertigo as well as headache, and practically all of the infants in this outbreak had convulsions. Nichamin (1945) recorded dizziness in 40 per cent of his seventy-five cases and also occasional disturbances in accommodation. Frank pleurisy, heretofore considered a rather rare complication, was encountered three times in the Brooklyn series, and there was an unusually high incidence of pharyngitis

also. Muscular tenderness and swelling often persist for several weeks after subsidence of the acute attack; Howard (1938) noted that in some instances defecation is more or less frustrated for a time by the excruciating pain. Children seem to be more susceptible to the disease than adults; no deaths in any age group have been recorded.

Rimpau (1938) said that this entity was first described by the Dane, Hannaeus, in 1735, and all students of the subject agree that it was observed in

outbreaks have been recorded in England (where Pickles' graphic accounts show how puzzling the attacks may be unless this entity is borne in mind), Denmark (Sylvest's monograph, now available in English, is very excellent), Sweden, Finland, Germany, Portugal, New Zealand, Switzerland and numerous parts of the United States. Since this is a summer disease and often attacks several members of a family at about the same time, some observers have looked upon it as a variant of poliomyelitis while others have thought of it as atypical dengue or at any rate as being mosquito borne; but these surmises remain uncorroborated. It was reported by the U.S.P.H.S., in 1944, that experimental indications of the virus nature of the disease had been obtained, *but I have seen no report of substantiating studies.*

THERAPY

The patient wishes to lie undisturbed, as every movement of the trunk

(0.3 gm.), antipyrine (phenazone, B. P.) 5 grains (0.3 gm.), acetylsalicylic acid (aspirin), 10 grains (0.6 gm.), have all been used at three- to four-hour intervals. In the more severe cases these drugs are not at all effective and opiates must be resorted to, but before giving morphine or dilaudid one might *try a few doses of the following combination,* cutting the amounts in half for children under fifteen years:

℞ Codeine phosphate		
Phenobarbital		
Extract hyoscyamus	āā gr. vj	0 4
Acetanilid	gr xxxvj	2 3
Divide into 12 capsules.		
Label 1 capsule every three hours		

ERYSIPELAS

Erysipelas is an acute disease characterized by a spreading erythematous skin lesion plus more or less severe constitutional symptoms. It is known to be caused by the beta hemolytic streptococcus, the organism probably in many instances entering through a preexisting skin abrasion. Mucous membrane cases are rare. Active adults in the middle decades, persons who have recently under[illegible]
most frequent
to the disease

because of some nasal or other focus of infection or because the skin remains hypersensitive to the organism) and have many attacks during their lives. In adults the face is perhaps more often affected than any other portion of the body, but in the newborn the infection often begins in the umbilical region, at the site of a forceps abrasion or an impetiginous lesion, or commonly in the diaper region, in later infancy it more commonly begins from an otitis media, acute rhinopharyngitis, or impetigo. Before the institution of sulfonamide [illegible]

up to two years of age.

[illegible]

demarcated and elevated border, small, flamelike extensions along the lymphatic channels are usually seen beyond this border. There is often a scattering of small vesicles throughout the affected area. The lesion spreads rapidly, and as it extends the earlier affected portions subside and desquamate. Sometimes localized abscesses, or necrotizing ulcers from secondary infection, form in the border, or the whole region may be undermined with pus Pain, often quite severe, is of the burning order. The swelling in typical cases is very considerable. Fever usually persists for two or three days and then falls by lysis or crisis, usually several days before the complete subsidence of the skin symptoms. However, one cannot make any definite prediction in regard to the course of the fever, and indeed the whole clinical picture may persist, with relapse after relapse, for several weeks instead of the usual duration of four to eight days.

This disease, though contagious and serious enough, does not tend to bec[illegible] medical writers thr[illegible] [illegible]alen mistakenly acc[illegible] It is extremely likely that some of the cases of ergotism, which were so numerous during the Middle Ages, were really this disease. Fehleisen showed the streptococcus to be causative in 1883

THERAPY

Sulfonamides.—These agents have rendered all the older methods of therapy completely antiquated. There are numerous careful studies available, but none of them are very recent for the reason that the efficacy of the sulfonamides is nowadays taken so much for granted that men are no longer concerning themselves with printed proof of the fact. The following are among the chief reports that established the position of the sulfonamides. Hoyne *et al.* (1939) reduced erysipelas mortality in Cook County Hospital to 2 46 per cent including all types and age groups and even deaths which occurred shortly after admission. Nelson *et al.* (1939) compared the results at Bellevue Hospital as follows: in 406 patients treated with erysipelas antitoxin the mortality for adults was 9.2 per cent, for children 37.5; in the group of 344 sulfonamide-treated cases these figures were respectively 1.5 and 12 9 per cent; Snodgrass *et al.* (1938), in England, reported a total mortality rate

limited course. Griswold and Bowen (1944) applied solid carbon dioxide with firm pressure to the lesions for two to four seconds, several centimeters of the apparently uninvolved tissue peripheral to the area of infection being also similarly treated. The treatments were repeated at intervals of one or two days, depending upon the presence of vesiculation or bullae from the previous application, and it was said to be rarely necessary to use more than three applications. The discomfort following the application of solid carbon dioxide was controlled by the use of salicylates internally. Fifteen cases were treated by this type of cryotherapy with no loss of time from work in any case beyond the first day of treatment and with an average duration of infection of four and two-thirds days and no duration longer than nine days in any instance.

FOOT-AND-MOUTH DISEASE

Foot-and-mouth disease is a highly contagious malady of domestic cloven-hoofed animals; Hull (1941) said that dogs, cats and poultry may occasionally become infected. The guinea pig is the animal preferred for the study of the disease in the laboratory. The malady is caused by a filtrable virus which is sometimes transmitted to man through the medium of infected milk or milk products or contact with diseased animals. The human cases are rare and transmission from man to man doubtful; indeed the great resistance in man was clearly shown in 1908 when smallpox virus vaccine contaminated with foot-and-mouth disease virus was widely distributed in the United States without the occurrence of a single human case. Among livestock the disease is widespread in Europe, South America and other parts of the world; the United States has several times experienced severe epidemics, which have been stamped out by mass killing, immediate burial and rigid quarantine. Studies in England have shown that dressed carcasses of infected animals may retain their infectivity even after ten weeks of refrigeration.

That great man, Girolamo Fracastoro (1484–1553)—who wrote the first complete description of syphilis, foresaw clearly the modern conception of the bacterial causation of disease and performed many other feats of original genius—described the first recorded epidemic of foot-and-mouth disease. And, indeed, since his time there has not been a great deal written upon it in the strictly medical press. In 1898, Loeffler and Frosch proved experimentally that the malady is caused by a filtrable virus; indeed, this was the first disease proved to be caused by an agent of this sort. I give Clough's summary of the symptoms: "A mild febrile infectious disease, characterized [illegible] with subsequent desquamation; and by healing of the ulcers [illegible] formation." Diagnosis is accomplished by inoculating blister fluid into the scarified skin of a guinea-pig's foot.

THERAPY

Treatment consists in the use of antiseptic mouth washes such as 1:2000 potassium permanganate. The silver nitrate stick may be applied to the ulcers just as in the treatment of canker sores. I imagine the lotion of cala-

mine and zinc (see Index) would be soothing when applied to the lesions on the body surface, and an ointment containing about 0.5 per cent holocaine (phenacaine) would allay mucous membrane pain. Very little has been written about the treatment of the disease, all attempts to influence its course by the intravenous introduction of dyes or other antiseptic substances have usually not succeeded, but von Scheitz (1934) stressed the beneficial effects of neoarsphenamine. I have seen no account of the successful employment of a sulfonamide or of penicillin.

GAS GANGRENE

(Clostridial Myositis)

Gas gangrene is caused by one of several clostridial organisms, the chief of which are *Clostridium welchii*, *Cl. oedematiens* (*Cl. novyi*), and *Cl septicum* (*vibrion septique*), the pathogenicity of these organisms being associated with the elaboration of toxins. These bacilli are normally present in the feces of animals and man and hence are widely distributed in soil throughout the world, they have also been recovered from clothing, room sweepings, glass syringes and from numerous other sources They have been recovered from the apparently normal organs of the genito-urinary tract, from surgically extirpated gallbladders and from wounds in which there was no clinical evidence of gas bacillus infection. However, under certain abnormal environmental conditions the organisms take on pathogenic propensities and give rise to a toxemia with extremely high mortality. In ordinary civilian practice these conditions are encountered most frequently in traumatic surgical cases but such occurrences are also not unknown in intestinal perforation, intestinal obstruction, gangrenous appendicitis, or in surgical conditions of the genito-urinary tract. Thornhill (1946) reported a primary infection in the unborn fetus, with the fetus dying but the mother surviving; it has also been reported following the injection of various therapeutic substances, most commonly epinephrine (adrenaline). But first and foremost gas gangrene is a complication of wounds received in battle. The deep wound from which air is excluded and in which there is partially devitalized tissue, especially muscle, is the site in which these organisms grow fast; the presence of foreign bodies or of other bacterial toxins or anything tending to promote necrosis aids establishment of *Cl welchii*. Once the focus is established the infection may remain localized in the wound or it may spread into a single muscle or a group of muscles or involve a large segment of the limb, or indeed there may be a general spread in all directions in extremely severe cases. Experience in War II abundantly confirmed the earlier impression that gas bacillus infections occur most frequently in the buttock and then the thigh and much less frequently in the shoulder girdle and the upper and lower extremities, the buttock infections are especially dangerous. It is ordinarily considered that when gas gangrene has set in the wound will quickly take on a distinctive appearance, becoming swollen with a serosanguineous fluid having a characteristic mousy odor and taking on a yellowish hue with purple and green patches; it has been thought too that palpation of the wound and even of the surrounding tissues at some distance removed from it elicits crepitation as a sign of the presence of gas in the tissues. However, Mac-

Lennan (1944) pointed out, as a result of extensive experience in the Mediterranean area in War II, that the presence of gas is a variable and in itself a valueless criterion of clostridial infection of muscle, and that the constant features are pain, swelling, and toxemia; of these pain, being the first to appear, is of the greatest significance. In fact MacLennan felt it not too much to say that, in wartime, the *possibility of an anaerobic myositis* must always be borne in mind when there is a sudden and unexplained onset or increase of pain in an infected wound. Langley and Winkelstein (1945), from extensive experience in evacuation hospitals in France, stressed also the anemia, which is disproportionate to the amount of hemorrhage but in *definite relationship to the length and severity of the toxemia.* The rise in temperature is often only moderate but the greater proportionate increase *in pulse rate* is a more valuable index to the degree of the toxemia In MacLennan's forty-four cases the incubation period varied from five hours to twenty-nine days, but if one excludes the exceptional case of twenty-nine days the average of the other forty-three cases was 1.6 days; no correlation was discerned between the length of the incubation and the clinical picture, the degree and type of injury, the nature of the bacterial flora, or the ultimate outcome.

THERAPY

Of all the features of treatment the most important seem to be accurate diagnosis, good surgery and intensive serotherapy The mortality rate of 11.5 per cent in Langley and Winkelstein's series of ninety-six cases cannot be directly compared with the 30 per cent in MacLennan's forty-four cases because of the difficulty of reconciling many features in the two series.

Surgery.—What constitutes good surgery in a given case will of course depend upon the condition of the patient and obviously cannot be described by me. At times apparently it may suffice to lay the affected area wide open, at other times complete excision of the wound and removal of the injured or infected tissues seem necessary even though this will lead to the sacrifice of a whole group of muscles; in many cases high guillotine amputation has to be resorted to.

Serum (Antitoxin).—The British school of investigators—Macfarlane and MacLennan (1945), Cooke *et al.* (1945)—is interestingly concerning itself with the possibility that the products of tissue breakdown may be a more important factor in the systemic reaction than is the circulating toxin of *Cl. welchii* However, since we are at present only provided with an antitoxin *against the latter, it is* with it alone that we can concern ourselves here.

Preoperative Employment of Antitoxin.—Since the rationale of the administration is to neutralize the circulating toxin, the agent must be given as long as toxemia persists. MacLennan and Macfarlane (1944) felt that the first dose should be given intravenously and as soon as possible, not delaying [illegible] lyva-
ating
very
profitable, but it must be admitted that they tried it in very few cases.

Postoperative Administration.—The serum should be administered in amounts and at intervals that seem indicated until a decrease in pulse rate indicates a satisfactorily diminishing toxemia. MacLennan and Macfarlane found it preferable to give the antitoxin *in small volume intravenously*

rather than to spread out the dose over many hours in a continuous drip, but Langley and Winkelstein (see General Postoperative Procedure below) favored the continuous drip. It is important to remember that even when the main source of infection has been removed by excision, the production of toxin may continue in small inaccessible remnants of necrotic tissue and that therefore the indication for the continued use of serum may persist.

Antitoxin Locally.—As the result of a histological study of muscle lesions, Robb-Smith (1945) suggested that local injection of antitoxin might be useful where it is proved impossible to perform an adequate surgical excision of the affected tissues, but I have seen no report of a clinical adoption of this suggestion.

Penicillin and Sulfonamides.—It is now the consensus that the sulfonamides are ineffective either in preventing the onset of gas gangrene or in limiting its spread, but since their general efficacy against other wound contaminants is easily recognized they are still usually routinely employed

be continued until granulations have formed on the wound surface, is probably almost universally acted upon, but Langley and Winkelstein (1945) did not feel that the preoperative employment of penicillin exerted any major effect in preventing infection, decreasing severity or preventing spread; they were convinced, however, that given systemically in large doses postoperatively it helped in reduction of both the duration of illness and the mortality. In twenty-two cases these latter observers also employed 33,000 to 100,000 units mixed with sulfanilamide and placed in the wound and felt that this treatment shortened the duration of the postoperative course and made it less stormy Gledhill (1945) entertained the same opinion of the efficacy of both the systemic and local employments of penicillin

Transfusion.—In gas bacillus infections there is usually profuse serous oozing from the wound site and a severe and progressive toxemia manifesting itself principally by circulatory failure and collapse—all of this often superimposed upon the hemorrhage and shock associated with the original wound. It is therefore easy to agree with MacLennan (1944) who said that it would be hard to exaggerate the importance of transfusion therapy in gas gangrene. Of his forty-four cases, forty-one were given blood, plasma or glucose-saline, usually in very large amounts, and had the other three pa-

(1945), stressing the severity of the anemia, were convinced of the greater usefulness of whole blood. It may be well to warn the reader against an error into which he may fall, namely, that of persisting in the administration of blood or plasma until extravagantly large amounts have been given in the belief that it is primarily shock rather than toxemia which is sapping

1. Sensitivity test for horse serum immediately on return to postoperative ward.

2. Nine therapeutic doses of gas gangrene antitoxin in 700 cc. physiologic saline by continuous intravenous drip for three hours; 40,000 units of penicillin introduced through the rubber tubing at the site of infusion. (A "therapeutic dose" means the amount of trivalent gas gangrene antiserum that contains 10,000 units each of the antitoxin for *Cl. welchii* and *Cl. septicum* and 1500 units of the antitoxin for *Cl. oedematiens.*) A rest period of from three to four hours to observe the effects of the antitoxin. If anemia is present, 500 cc. of whole blood to be transfused at this time.

3. Repetition of "2" until signs of toxemia begin to abate, no limit being set on the number of therapeutic doses of antitoxin to be administered.

4. Penicillin 20,000 units every two hours together with sulfadiazine 1 gm. every four hours or, if the oral route is not available, 10 to 15 gm. of sodium sulfadiazine intravenously per day. A minimum of 720,000 units of penicillin, not including that given intravenously, should be completed by the intramuscular route before therapy is completed.

5. One therapeutic dose of antitoxin every twelve hours intramuscularly after the completion of the intravenous therapy for a minimum of four injections.

6. Hemoglobin, red blood cell count, hematocrit, fluid intake and output checked daily; whole blood as necessary.

Zinc Peroxide and Oxygen.—The first of these agents has a good record in experimental gas gangrene infections but I have seen only one report of its employment in the human. Hudson and Rucker (1945) treated a case of postabortal infection with penicillin, which apparently confined the infection to the uterus but had no effect upon the process within that organ. The addition of sulfadiazine by mouth and local treatment with zinc peroxide seemed to save the situation. The zinc peroxide was given as a paste by intrauterine douche, the foot of the bed being elevated during the procedure. Hinton (1947) reported apparently good results in one case from the subcutaneous and intramuscular injection of oxygen at many sites about $1\frac{1}{2}$ inches beyond the advancing edge of the lesion.

GERMAN MEASLES

(Rubella, Rotheln)

This highly [illegible] but is distinct from [illegible] virus present in the [illegible] is will not be gone into here; suffice it to say that an outstanding feature of the disease is an adenitis of the mastoid, occipital, cervical, and often the inguinal and axillary glands. Complications are not often seen. purpura has been reported in a few instances; Logue and Hanson (1945) reported a case of complete heart-block of short duration during the pre-eruptive stage; Wingo (1945) reported an instance of complicating encephalomyelitis, bringing the total number of such reported cases to fifty-one, in which the combined fatality rate was 19.6 per cent. The average *incubation period is* usually considered to be fourteen to twenty-one days, usually about sixteen days; in Pickles' (1942) cases in which he could be positive of the only possible exposure, the incubation periods ranged between fourteen and seventeen

days. An attack of measles seems to predispose to infection with German measles; bona fide second attacks are quite rare. During an epidemic of unusual severity in Australia in 1940, abnormalities including cataracts, deaf-mutism, heart disease, microcephaly and mental retardation were observed in distressingly many instances in infants born to mothers who had suffered from German measles during their pregnancy; indeed, the data gathered by Swan *et al.* (1943) suggested that the chances of giving birth to a congenitally defective child when a woman contracts German measles within the first two months of pregnancy are almost 100 per cent and that if she contracts the disease in the third month they are about 50 per cent. In the time since attention was attracted to this coincidence of congenital anomalies and maternal German measles in Australia, numerous instances of the sort have been reported fron [illegible] s at first suggested that [illegible] tralia during the perio [illegible] e herded together in military camps there, but increasing experience makes it seem likely that it is not a particularly virulent virus which is causing these cases but that ordinary German measles does cause fetal damage. Conte *et al.* (1945) collected 141 cases, in all save four of which the rubella occurred in or before the third month of pregnancy and in the exceptions it occurred in the fourth, fifth, sixth and seventh months. Aycock and Ingalls (1946) felt that on the basis of the admittedly incomplete data of their own study and that of Fox and Bortin (1946) the risk of anomalies in infants [illegible]

representing the risk. Surely to arrive at definite knowledge of how often the congenital anomalies truly follow upon maternal rubella in early pregnancy some obstetrical-pediatric team of investigators will have to start at the other end of the line, *i e.*, by making the diagnosis of rubella in mothers and then recording the number followed by anomalies in the infants. Aycock and Ingalls (1946) had personal knowledge of four cases in which death of the fetus and spontaneous abortion apparently resulted from rubella infection in the mother.

THERAPY

German measles is ordinarily such a mild affair that not much thought had been given to its prevention until the recent recognition of the danger to the fetus of a mother who contracts the disease during early pregnancy. The only available measure in such cases is the employment of immune gamma globulin, though its efficacy has not been established. A number of authors have gone so far as to propose therapeutic abortion in all mothers who contract rubella in the early months of pregnancy, but many other men certainly feel that we do not as yet have justification for such a radical step; the position of the latter seems to be justified since the risks to the infant of infection in various stages of pregnancy are not definitely known. Then, too, in assessing this matter it is important to look into the possible role of the other virus diseases also. Lynch, as long ago as 1932, called attention to the high mortality of the fetus in maternal measles and smallpox, and Swan (1944) postulated that more severe virus infections, such as measles, may kill the fetus whereas the milder

German measles merely damages the surviving fetus. Aycock and Ingalls' (1946) study of the records of 264 cases of maternal poliomyelitis suggested that the risk to the fetus is high if the disease occurs in the first three months of pregnancy, though it was not clear to what extent the hazard may be the result of paralysis in the mother. The above authors also said that in collecting data on prenatal disease in relation to mongolism they had found that of fifty mongols there were five instances when a specific, relatively incisive maternal illness was present at the eighth week of gestation, and five others in which a more chronic maternal disorder included the eighth week of fetal life.

At the present time it would seem that the only available measure of positive value would be the deliberate exposure of female children if they have not contracted the disease by the time of adolescence; but perhaps the belated recognition of the seriousness of this whole problem will spur investigators on to the development of satisfactory methods of inducing attenuated forms of some of the virus diseases at will through inoculation. In connection with deliberate exposure to rubella, Aycock and Ingalls (1946) pointed out that there is a mortality of 1:30,000 to 1:100,000 to be reckoned with, but since this mortality is to be found in all age groups they felt that the menace the disease holds for the unborn child would be appreciably reduced if not eliminated by suitable inoculation.

GIARDIASIS

(Lambliasis, Flagellate Dysentery)

In recent years it has become generally recognized that infestation of the intestinal tract, particularly of the duodenum and upper part of the ileum, [illegible]

[illegible] ...ptoms. It would seem that, [illegible] by the frequent passage of [illegible] nd foul odor but only very rarely containing a little mucus or a tinge of blood, is the disturbance most frequently associated with this infestation, it would probably be wise to con- [illegible]

[illegible] *G. intestinalis;* however, the improvement in patients who are rid of their infestation by the employment of atabrine (see below) strongly supports the [illegible]

[illegible] children, is of no clinical interest; that heavy infestations of the colon when [illegible]

characterized by a periodicity of symptomatic episodes. Welch's (1943) study indicated that eosinophilia may be characteristic of severe giardial infestation. In Drenckhahn's (1943) case there was jaundice associated with the presence of large numbers of the flagellate in the bile content. Similar but perhaps not entirely identical forms of this organism infest many domestic animals

THERAPY

Until recently in giardiasis the whole gamut of amebacidal and anthelmintic drugs had been run without much success, but now it seems that a truly specific agent has been found in the synthetic antimalarial drug atabrine (quinacrine, mepacrine). Galli-Valerio (1937) first reported its successful use in Switzerland and quickly thereafter confirmation came from practitioners in several other countries. Hartman (1943) said that at the Mayo Clinic approximately seventy-five patients had been treated with but one failure from one course

epidemic of gastro-enteritis, reported by Freedman (1946), the condition was

infestation. It is now customary in the practice of many men to give two and sometimes three courses of treatment with an interval of a week or ten days

affect the absorption of vitamin A.

In a patient who did not completely clear up upon one course of atabrine, Schindel (1945) successfully used diodoquin as in amebiasis (*q v.*). Berberian (1945) also successfully used acranil, a compound closely related to atabrine, but his dosage was still experimental

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GLANDERS

(*Farcy, Malleus*)

with the organism is very great, as was dolefully reemphasized in Prague, in 1924, when three well-known scientists succumbed to the disease within a brief

period. The outbreak which they were investigating claimed in all 7 deaths (in 7 cases), all deriving from one infected horse. Upon the other hand man seems to be quite resistant to infection under ordinary conditions. Hull (1941) cited an instance in a road construction camp in Illinois in which 19 horses died of the disease and some 50 more infected animals were killed but among the 600 or 700 men in camp who had been in more or less close contact with the animals only 1 case developed. Acute glanders in man may begin with symptoms indicative of almost any of the other infectious diseases, which makes early diagnosis very difficult; however, Symmers says: "The occurrence of symptoms of an acute infective disease in an individual who comes in contact with horses and who presents multiple abscesses in the skin or in the mucous membrane of the nose, with deep-seated pain or tenderness, indicative of abscesses in muscle tissues, tendon sheaths, fascia or periosteum, with or without joint symptoms, should suggest the diagnosis of glanders in spite of the extreme rarity of the disease, and confirmation should be sought in isolation of the causative bacillus and guinea-pig inoculation" There is also a chronic [illegible]

[illegible] pital for pneumonia and diagnosed as glanders only several weeks later after a [illegible]

troublous years, was either anthrax or glanders. Solleysel described the transmission of the disease from horse to horse in 1664 The classical monograph on the disease in man is that of Rayer, in 1837. Loeffler discovered the causative organism in 1882.

THERAPY

There is no admittedly specific treatment for glanders in man, though [illegible]

description here; they are such as are applied in any other fulminating condition. It is said to be advisable to excise the local nodule where possible, though in an outbreak, in 1926, of seven cases in eastern Austria, five terminated fatally in spite of the fact that the original focus was eliminated in each case.

INFANTILE DIARRHEA AND VOMITING

In the good old days when privies were neatly whitewashed and there were still plenty of corner pumps and horses and flies, and when the milkman drove about ringing his big bell in the heat of the day and ladling his wares from open cans into nicely sun-warmed pitchers and jugs—in those far-off times a goodly [illegible] nths of [illegible] ged and [illegible] modern civilization, but nonetheless infantile diarrhea and vomiting is [illegible] seen distressingly often throughout the year, particularly in artificially-fed infants and

some instances the symptoms are definitely secondary to infection elsewhere. Mortality is still high unless expert therapy is begun very early.

THERAPY

Sulfonamides.—The sulfonamides have been used with considerable success in many of these cases in recent years. There seems to be no advantage in using the non-absorbable members of the series, such as sulfasuxidine and sulfathal-

twenty-four-hour dose immediately and the rest in equal portions every four hours.

Fluids and Alkalis.—The reader should mark well that the favorable employment of the sulfonamides in the treatment of infantile diarrhea and vomiting is predicated upon the understanding that despite the use of these agents dehydration has to be vigorously combated in the beginning in all severe cases The usual routine is to give intravenously 5 per cent dextrose solution, or physiologic saline solution, or 5 per cent dextrose in the saline, the fluid should be introduced at the rate of 15 to 30 drops per minute for the first 200 or 300 cc but thereafter the rate must be cut down rather sharply; Alexander and Eiser (1943) said that infants under three months require a slow flow of 8 to 10 drops per minute while older children will tolerate 12 to 15 drops per min

as puffiness of the hands and feet, eyes, scrotum or vulva, the fluid must be immediately discontinued since an infant can be easily "drowned" with parenteral fluid. Acidosis must oftentimes be combated also, but Mitchell (1939) well pointed out that the routine administration of sodium bicarbonate to all infants with diarrhea is unjustified since actual alkalosis may thus be caused and the diarrhea may be increased if the alkali is given by mouth. Indeed, Mitchell advocated alkali administration only if determinations of the carbon dioxide content of the blood indicate its necessity—but such determinations are certainly not possible in all types of practice. In general, coma or impending coma, hyperpnea or convulsions (but the latter may also indicate that too much alkali has been given) are good indications that the [illegible]

period. The outbreak which they were investigating claimed in all 7 deaths (in 7 cases), all deriving from one infected horse. Upon the other hand man seems to be quite resistant to infection under ordinary conditions. Hull (1941) cited an instance in a road construction camp in Illinois in which 19 horses died of the disease and some 50 more infected animals were killed but among the 600 or 700 men in camp who had been in more or less close contact with the animals only 1 case developed. Acute glanders in man may begin with symptoms indicative of almost any of the other infectious diseases, which makes early diagnosis very difficult; however, Symmers says: "The occurrence of symptoms of an acute infective disease in an individual who comes in contact with horses and who presents multiple abscesses in the skin or in the mucous membrane of the nose, with deep-seated pain or tenderness, indicative of

[illegible]

of the causative bacillus and guinea-pig inoculation." There is also a chronic form of the disease which must be differentiated (Burgess, 1936) from granuloma inguinale, lymphogranuloma inguinale, tuberculosis of the skin, syphilis and mycotic and yeast infections; Hull (1941) cited a case admitted to hospital for pneumonia and diagnosed as glanders only several weeks later after a positive laboratory examination, and Panja and Chatterjee (1943) described a case which had been mistaken for smallpox.

It is thought that the strange affliction of animals and men during the ninth to twelfth centuries, called *malum malannum* because of its recurrence in troublous years, was either anthrax or glanders. Solleysel described the transmission of the disease from horse to horse in 1664. The classical monograph on the disease in man is that of Rayer, in 1837. Loeffler discovered the causative organism in 1882.

THERAPY

There is no admittedly specific treatment for glanders in man, though Howe and Miller (1947) felt that their results with sulfadiazine in six cases warranted further adequate trial of the agent. The palliative measures directed to the relief of the general constitutional symptoms do not merit special ... applied in any other fulminating condi- ... ough ... nated fatally in spite of the fact that the original focus was eliminated in each case.

INFANTILE DIARRHEA AND VOMITING

In the good old days when privies were neatly whitewashed and there were still plenty of corner pumps and horses and flies, and when the milkman drove about ringing his big bell in the heat of the day and ladling his wares from open ...

[illegible]

civilization, but nonetheless infantile diarrhea and vomiting is still distressingly often throughout the year, particularly in artificially-fed infants and

especially among the poor and less well-nourished classes. The etiology of these cases is complex: some seem due to dietary errors, doubtless many are really cases of bacillary dysentery, in some instances there is infection with a member of the *Salmonella* group or with a streptococcus or some other organism, in some instances the symptoms are definitely secondary to infection elsewhere. Mortality is still high unless expert therapy is begun very early

THERAPY

Sulfonamides.—The sulfonamides have been used with considerable success in many of these cases in recent years. There seems to be no advantage in using the non-absorbable members of the series, such as sulfasuxidine and sulfathal- [illegible] bable [illegible] has [illegible] this series are employed is 0.1 gm. per kg of body weight (1½ grains per 2 2 pounds) per twenty-four hours, the patient usually being given one half of the initial twenty-four-hour dose immediately and the rest in equal portions every four hours.

Fluids and Alkalis.—The reader should mark well that the favorable employment of the sulfonamides in the treatment of infantile diarrhea and vomiting is predicated upon the understanding that despite the use of these agents dehydration has to be vigorously combated in the beginning in all severe cases The usual routine is to give intravenously 5 per cent dextrose solution, or physiologic saline solution, or 5 per cent dextrose in the saline; the fluid should be introduced at the rate of 15 to 30 drops per minute for the first 200 or 300 cc. but thereafter the rate must be cut down rather sharply; Alexander and Eiser (1943) said that infants under three months require a slow flow of 8 to 10 drops per minute while older children will tolerate 12 to 15 drops per minute, but certainly the rate of flow and the total quantity of fluid given need to be adjusted for the baby's weight, the degree of dehydration, the amount of pyrexia and the amount of fluid which the infant is taking by mouth. One must watch these patients very carefully, too, and at the earliest sign of edema, such as puffiness of the hands and feet, eyes, scrotum or vulva, the fluid must be immediately discontinued since an infant can be easily "drowned" with parenteral fluid Acidosis must oftentimes be combated also, but Mitchell (1939) well pointed out that the routine administration of sodium bicarbonate to all infants with diarrhea is unjustified since actual alkalosis may thus be caused and the diarrhea may be increased if the alkali is given by mouth. Indeed, Mitchell advocated alkali administration only if determinations of the carbon dioxide content of the blood indicate its necessity—but such determinations are certainly not possible in all types of practice In general, coma or impending [illegible]

some instances these quantities may have to be greatly exceeded. The sodium bicarbonate may be administered in 5 per cent solution intravenously, or 1/6 molar sodium lactate solution (which is higher in sodium lactate content than Hartmann's solution) may be used instead; the lactate solution has the advantage over sodium bicarbonate solution that it can be sterilized by boiling.

[illegible]

desquamation were encountered in their series and were held to be attributable to the employment of potassium, it would seem that this innovation in therapy is still in the experimental stage.

Diet.—It is almost the rule to starve the patient for twenty-four hours (some pediatricians permit very weak tea with saccharin) and then to begin [illegible]

twelve hours after admission to the ward they offered full bottles to their infants and gave them as much as they would take, the orders reading "buttermilk as tolerated" or "skimmed boiled milk ad libitum" These observers found that the children regulate their intake according to their appetite, and they find it a great advantage to be able to tell the mother to allow the infant to take as much as he wants. Upon cessation of the diarrhea, *i.e.*, when the stools have been normal from two to four days, they return the infant to the normal formula during a period of twenty-four to forty-eight hours by replacing fractions of buttermilk by formula.

Bismuth and Opiates.—During the height of the diarrhea many men employ a bismuth and paregoric mixture such as the following:

℞ Camphorated tincture opium	ʒi	4.0
Bismuth subcarbonate	ʒi	4.0
Mucilage acacia	℥i	30.0
Anise water to make	℥iv	120.0

Label: For infant up to two years, 1 teaspoonful every three hours.

However, most pediatricians decry this practice and resort to the use of these drugs only in extreme cases.

Treatment of Shock.—In some instances a severely dehydrated baby may be collapsed when first seen and will require to be treated as described in the article on Shock. Alexander and Eiser (1944) found that in administering serum or plasma to infants it is simpler to use one-half strength solution to obviate the technical difficulty of getting the rather sticky full-strength fluid to run through a slow drip; they also warned against too enthusiastic serum or plasma therapy in small infants, reporting four consecutive cases in which the continuous infusion of half-strength serum caused so much tissue fluid to be drawn into the blood stream as to initiate serious circulatory embarrassment. Darrow's (1946) recommended dosage, before dilution, was 20 to 30 cc. per kg. (2.2 pounds).

Apple (or Banana) Diet.—In Germany some years ago there developed out of an old folk remedy the so-called "Moro-Heisler apple diet" for the treatment of all sorts of diarrheal conditions in infants and young children. Ripe, mealy eating apples, cored and grated to a fine pulp (with or without previous paring) were given in quantities of 1 to 4 tablespoonfuls each hour during the day. If the acid flavor was objected to an inch of ripe mashed banana was added to each spoonful of apple. No other food was given. Patients took from [illegible] day and it would seem that the more the better. Ter- [illegible] after the appearance of formed or [illegible], but perhaps thirty-six or more,

hours after beginning it. Mitchell (1935) used the following transitional diets for a few days in bringing the patient back to full feeding:

	Infants	*Children.*
Breakfast.	Cooked cereal (no milk) Apple pulp (4 tablespoonfuls)	Cereal (with skimmed milk sufficient to make edible) Toast Cocoa (made with water)
Midmorning:	Apple pulp (1–4 tablespoonfuls)	Apple pulp Cracker (saltine or soda cracker)
Lunch:	Clear broth or bouillon Rice Junket (made from skimmed milk)	Broth or bouillon Rice Scraped beef or chicken Toast or cracker Junket (from skimmed milk)
Midafternoon:	Gelatin	Gelatin and cracker
Supper:	Cooked cereal Apple pulp	Cooked cereal Toast Cocoa Apple pulp or banana

Skimmed milk, whole milk junket, baked potato, custard, jam, marmalade and cream cheese may be added next. Cream is gradually returned to the milk,

weak tea or skimmed milk, 24 to 36 gm. for infants under one year, 80 to 100 gm for older children. Many men also replaced apple with banana with good success, and latterly banana powder more or less replaced the fresh fruit.

these diarrheas. This seemed adequately to replace apple or banana, fresh or powdered, and to be very simple to use The ingredients of this preparation, as described by Howard and Tompkins (1910), are pectin 6.3 per cent, agar 4.3 per cent, dextri-maltose 89.4 per cent One cup (8 ounces) of this powder

ones it should be fed in only half the usual quantities, fluid being administered otherwise. For children six months to two years, 8 ounces of the powder is cooked with only 16 ounces of milk, or it may be cooked in a smaller amount of water and fruit juices added up to full volume; flavoring agents such as vanilla or chocolate may be added, and the mixture may be frozen if preferred.

INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM JAUNDICE

As commonly encountered, infectious hepatitis is mildly epidemic in children and in young adults Neefe's (1946) analysis presented strong evidence that susceptibility to infectious hepatitis is high between the ages of six and twenty-five and rapidly decreases after twenty; however, middle-aged and even elderly patients are not infrequently seen, and racial and sexual differences in susceptibility are not apparent The disease seems to have a seasonal trend, cases increasing during the fall and early winter and decreasing during the late winter and spring But in times of war it has often been recorded in [illegible]

Northern troops. The French have referred to the disease as the "Jaundice of Camps" and the English have often called it the "Jaundice of Campaign." In War I there were 2195 cases in British troops in the Mesopotamia and Dardanelles region in the fall of 1915, and in War II it was epidemic among the forces on both sides and in practically all theaters. Sapero (1946) reported that 191,574 cases had been diagnosed in our own Armed Forces, thus constituting this entity the third most frequently encountered infectious disease, being outranked only by dysentery and malaria. Capps and Barker (1947) said that in their extensive experience with the disease here in the United States, both in the Army and among civilians, they found no essential differences from the form they studied in Africa, Italy, France and the Near East during the War; others have more informally reported in the same vein regarding the [illegible]

(b) Marchand (1943) recounted that in an isolated Indian village in the Yukon territory brought into contact with the outside world by the construction of the new Alaska military highway, epidemics of measles, dysentery, whooping cough, mumps, meningococcal meningitis *and* infectious hepatitis broke out among the inhabitants; (c) the demonstration by Findlay and Willcox (1945) [illegible] volunteers by the oral ingestion [illegible] Neefe and Stokes (1945), the [illegible] t was water-borne, the outbreak being the result of *fecal contamination of the drinking water.* Neefe (1946), Gauld (1946), and others feel it quite possible that respiratory spread may account for many of the infections though the experimental evidence [illegible] the findings respecting [illegible] per cent of the inhabi- [illegible] d Hanlon (1946), it was said that the risk of contracting hepatitis for members of the household of a primary case was as great or greater than a similar risk in scarlet fever, *diphtheria* or bacillary dysentery. Gauld (1946) found that seasoned troops who had passed through one infectious hepatitis epidemic were less *susceptible* than reinforcements who had not previously been exposed to the *disease.* Indeed, it would seem that one attack of infectious hepatitis usually confers a relatively permanent resistance to reinfection. Neefe (1946) feels that the causative virus may be sufficiently widespread to immunize most of the popu-

jaundice is that reported occasionally in association with the employment of measles and mumps convalescent serum, of glycerinated humanized smallpox lymph and of whole blood or of reconstituted human adult serum and plasma In 1942 we had in the American Army an enormous number of cases of this type of jaundice associated with the employment of yellow fever vaccine in the preparation of which human serum had been used; the absence of cases in the Navy was due to the fact that by unusual chance none of the icterogenic lots of vaccine was received by them There are indications in the recent British literature, such as in the papers of Howells and Kerr (1946), and

infectious hepatitis, (b) infectious hepatitis has been transmitted experimentally by feeding stools and urine but serum jaundice has not been so transmitted; (c) volunteers recovered from either infection are susceptible to infection with the other virus; (d) recovery of the virus of infectious hepatitis from the stools of patients with homologous serum jaundice has not been accomplished

The symptoms of acute infectious hepatitis (or of homologous serum jaundice) are malaise, sometimes mild headache and dizziness, enlargement of the liver and sometimes of the spleen, occasionally pain in the liver region, nausea and perhaps vomiting—both these latter symptoms being especially marked if the patient refuses to go to bed—slight fever, or normal or subnormal temperature, slow pulse, jaundice, bile-stained urine and clay-colored stools, more or less general pruritus, and mental depression that is sometimes quite profound and is not infrequently associated with an unwonted irritability. Weinstein and Davison (1946) reported four cases with unmistakable signs and symptoms of dysfunction of the nervous system in the pre-icteric phase of the disease. The gastric symptoms usually persist for only a few days, but many patients suffer a return of nausea and dizziness if they attempt to assume the upright position at any time throughout the course of the attack. Bank and Dixon (1946) performed gastroscopy in forty-three patients and found no evidences of gastritis in either acute or chronic cases. The duration of an attack in adults is ten days to perhaps as many weeks, and some degree of jaundice often persists for a long time in a patient otherwise apparently quite recovered Occasionally the attack recurs However, though very debilitating in persons of military age and older, the disease is relatively innocuous in

cases involved in these outbreaks there were no examples of severe hepatitis with prolonged jaundice or of protracted convalescence. Horstmann *et al.*

pointed out that the difference between the severity of infectious hepatitis in children and in adults is comparable to the difference existing between childhood and adult forms of the other more common virus infections such as measles, mumps and chickenpox.

In some epidemics principally involving children there has been no mortal- [illegible]

[illegible] different epidemics the incidence of cases without overt jaundice is from 28 to 80 per cent of the total number of apparent infections. Death may occur during the first week of the disease or only after many weeks or even months of illness. There are observers who feel that mortality is much higher in the cases of homologous serum jaundice than in those of *infectious hepatitis*, but Berk (1947) well made the point, in an analysis of a considerable series of cases following transfusion, that the apparent higher mortality rate in these cases is probably ascribable not to the disease itself but to the impaired protein nutritional status of the patient who requires transfusion. Lucké and Mallory (1946) have published extremely interesting observations on a group of fatal cases possibly representing a new form of the disease to which they have applied the title "fulminant." Clinically these cases were characterized by a sharp and stormy course, the liver in some instances being destroyed completely and uniformly, and death occurring less than ten days. Ascites was [illegible] cases of fulminant hepatitis its [illegible]

nant form of hepatitis has been occurring in Denmark since 1944, that it is predominant in women over forty-five years of age, and that it has a fatality rate of 50 per cent. Most frequently this Danish form of fulminant hepatitis has a duration of from four to nine months, but Alsted said that both a much more acute and a much more protracted course is observed

Caravati (1944) reported that he had seen a rather large group of officers and enlisted men who, *as an apparent sequel to jaundice contracted in the* Army in 1942, exhibited a clinical syndrome that he designated "posthepatitis syndrome," the principal findings being fatigue, right upper quadrant [illegible] particularly fat intolerance, malnutrition [illegible] and Hoyt (1945), Sherlock and Walsche (1946), Flood and James (1947), and others have since reported series of cases presenting findings identical with those of Caravati The fact that psychoneurotic patterns may develop during hepatitis, or that antecedent patterns [illegible] Some of the patients [illegible]

the upper gastro-intestinal tract and the bile ducts and [illegible] of Vater plugged with mucus, this conception being, in the words of an anonymous recent writer, "one of Virchow's less fortunate contributions to pathology." Recently, however, the biopsy studies of Roholm and Iversen (1939) in Sweden, amplified and extended by Dible *et al.* (1943) and subsequently confirmed by Mallory (1947), Flood and James (1947), and others

here in the United States and elsewhere, have established the fact that there is really an hepatic lesion in these cases and no evidence of bile stasis as required in the older concept. Upon autopsy in fatal cases, Lucké (1944), and Mallory (1947), found in the liver without exception the changes typical of idiopathic yellow atrophy. Lucké also found complete restoration of hepatic parenchyma in fourteen individuals who recovered and later died of some other cause, and Mallory (1947) said that in all the postmortem material that had been submitted to the Army Institute of Pathology up to the time of his presentation there was not one definite case of cirrhosis [illegible]

[illegible] cations that in some cases the end stages of prolonged hepatitis may be indistinguishable anatomically from ordinary atropic or portal cirrhosis; these observers felt that evidence has been accumulating for a number of years strongly supporting such a relationship.

Neefe (1946), in an authoritative review, stated that the usual incubation [illegible]

malady an extreme range of one to six months There is some evidence that the disease is most highly communicable during the prodromal stage preceding the onset of jaundice

The point seemed to me to be strongly developed in the work of Capps *et al.* (1947) that the most important feature of laboratory diagnosis is the fact that the value of different procedures varies with the stage of the disease; for example, one of the best early tests is that for bilirubin in the urine, but this test is of almost no value later on because of an apparent increase in the renal threshold for bilirubin. Capps *et al* made the point that with specialized laboratory facilities not available the most satisfactory diagnostic measures are the methylene blue or the strip test for bilirubinuria, the acetone icterus index, the sulfobromophthalein sodium dye retention, and the quantitative urobilinogen test.

THERAPY

Capps and Barker (1947), basing their conclusions on a systematic study of over 2000 cases and the observation of some 6000 more, stated that there were only three major therapeutic principles of proved value in infectious hepatitis; these were bed rest, diet, and the avoidance of additional factors injurious to the liver

Bed Rest.—Failure of the patient to go to bed during the acute icteric stage may apparently cause a case of only moderate initial severity to progress to a fatal outcome over a period of weeks, in the convalescent stage, after [illegible]
becon [illegible]
induc [illegible]
Finally, it seems that patients put to bed during the first few days of illness are less likely to develop jaundice than those who remain ambulatory. It is obvious from the above that bed rest should be instituted as early in the disease as possible Capps and Barker said that in their opinion bathroom

privileges may be allowed to all who are not seriously ill, but that the bed rest regime should be maintained in all cases until the patient can satisfy the following criteria: (a) he shall have had at least three weeks in bed; (b) the liver should be neither enlarged nor tender; (c) there should be absence of symptoms, especially lassitude, diarrhea, intestinal cramps, flatus, headache and anorexia; (d) there should be normal serum bilirubin for one week, or if slightly elevated the direct van den Bergh must be *negative*; (e) bromsulfalein must be under 10 per cent in one hour (5 mg. per kg. being the dose) and preferably under 5 per cent. Also, if available, the cephalin cholesterol flocculation test should be 2 plus or less in twenty-four hours and the alkaline serum phosphatase under 4 0 Bodansky units. If only one finding is positive the patient should be kept in bed one extra week. These observers found in military practice that even when the above criteria for return to the ambulatory state are met, about 10 per cent of patients will show an abnormal exercise tolerance test; in civilian practice they felt that as a substitute for this test patients should be followed carefully for several weeks after returning to work to insure proper convalescence and determine if they have really recovered—failure to return the patient to bed immediately upon recurrence of positive findings they felt might lead to the establishment of chronic hepatitis.

Diet.—Capps and Barker felt that while there is ample experimental evidence that a diet high in protein is most desirable for acute liver injury, they do not believe there is sufficient evidence concerning the harmful effects of fat to warrant more than moderate restriction Wilson *et al.* (1946) compared the progress of fifty-two patients on a low-fat diet with that of fifty-one on a high-fat diet and found no significant differences in the rate of recovery in the two series. However, Capps and Barker found an excess of fat, other than butter fat, poorly tolerated and in some cases leading to anorexia. They felt that carbohydrates should be high in order to spare protein as well as to provide calories. For the average case they recommended a diet of protein 200 gm , fat 65 gm., and carbohydrates 300 gm. This amount of protein is readily obtained by the liberal use of skimmed milk powder and cottage cheese, and enough fat in the form of butter and cream must be employed to make the diet palatable. For the record, however, it should be stated that Darmady (1945) failed to demonstrate the superiority of a high protein-high vitamin B complex diet in a small but well controlled study. Richardson and Suffern (1945) gave 1.5 gm of choline chloride as a supplement to a low fat-high carbohydrate diet with the addition of vitamins to alternate cases in a series of thirty-two patients, no significant benefit of the special diet was observed. Wilson *et al* (1945) also failed in a controlled series of patients treated with methionine But in a series of fifty-two patients to whom they gave 5 gm. of cysteine daily by mouth there was produced what seemed to be a significant shortening of the period of recovery compared with fifty-one control cases not so treated; it seemed that the recovery occurred sooner because of a smaller number of relapses in the treated group. Capps and Barker (1947) said the addition of neither methionine nor choline produced clear-cut results in their experience

Avoidance of Additional Liver Trauma.—In the opinion of Capps and Barker (1947), the most common causes of additional trauma are surgical operations, secondary infections, and exposure to various toxic substances, notably alcohol. They felt that surgical operations are probably injurious

to the liver both because of factors incident to tissue trauma and because of the anesthetic; in cases of emergency, local or spinal anesthesia should be employed, ether, chloroform and possibly ethylene being likely the most dangerous anesthetics. Secondary infections of all sorts are said to have a deleterious effect in infectious hepatitis and the victim of this disease seems to have a very low resistance to such infections. Capps and Barker found [illegible]

should be combatt[illegible]
that are probably [illegible]
effect in the preser[illegible]
seen fatal morphinism after 1/2 grain (30 mg.) and that they had known patients to sleep for thirty-six hours after 3 grains (0.2 gm.) of amytal.
[illegible]

or indirect transmission of the virus from feces, using the sanitary and hygienic measures employed in control of enteric infections such as bacillary dysentery and typhoid fever. Although the interval during which the feces contain a virus is uncertain, such excreta tentatively should be regarded as potentially infectious for at least a month after the onset of the disease, and of course prevention of transmission by blood is also warranted and should consist in thorough sterilization of all syringes and needles after use on these patients And of course obviously blood from such patients should not be administered to others. Neefe said that although there is no direct evidence indicating the necessity of vigorous application of the measures generally used for prevention of respiratory transmission, still reasonable precautions should be taken

Gamma Globulin in Therapy.—The studies of Gellis, Stokes *et al.* (1945) failed to reveal that gamma globulin (see under Prophylaxis, below) had any attenuating effect when administered in the course of the disease.

PROPHYLAXIS

During an epidemic of infectious hepatitis in a summer camp for children, Stokes and Neefe (1945) injected gamma globulin intramuscularly and obtained results which they thought indicated that this agent will prevent or attenuate infectious hepatitis to a degree comparable to that observed when it is used in measles Their findings were subsequently verified in another study by themselves and in on[illegible]
of 10 cc. of gamma globulin, [illegible]
(0 5 kg.) of body weight, is [illegible]
of Robinson *et al.* (1946) the incidence and course of the disease were practically the same in two groups, one of 523 individuals given prophylactic globulin and the other of 449 individuals not so treated Duncan *et al.* (1947) reported a rather extensive and well-controlled study, the data from which suggested that a single injection of gamma globulin did not protect completely against homologous serum jaundice although it apparently delayed the onset of attacks.

INFECTIOUS MONONUCLEOSIS

(Glandular Fever)

This is an infectious and probably contagious disease characterized by intermittent or remittent fever which continues for from one or two days to three or four weeks, complaints of general malaise, sweats, sore throat,

nuclear leukocytosis and reduction in the number of neutrophilic granulocytes (polymorphonuclear cells) which gives a picture somewhat resembling that of acute leukemia without the anemia and usually without the platelet reduction characteristic of the latter. Limarzi *et al.* (1946) found a myeloid hyperplasia and immaturity in the bone marrow and suggested as an important differential point the absence of the replacement characteristic of leukemic cells in lymphatic leukemia. Some cases with visceral glandular enlargement simulate an acute abdominal emergency; meningitis may be suggested by the pain and spasm of the neck muscles, and indeed actual involvement of the central nervous system has been several times recorded. Conjunctivitis, jaundice with or without hepatomegaly and impaired liver function without jaundice, epistaxis, hematuria, rectal bleeding, petechial and purpuric hemorrhages—these and numerous other manifestations are recorded. In fact, Bernstein (1940), in his excellent review, said that on a modest scale infectious mononucleosis may be said to resemble syphilis in its ability to simulate other diseases; Rubenstein and Shaw (1944) found that it may readily be confused with brucellosis. Evanescent false positive serological reactions for syphilis have been reported by several observers. Anderson and Cox (1945) reported a very unusual case following a skin abrasion on the right leg and involving the lymph nodes only of the right inguinal region. Distribution of the disease is world-wide, the patients being chiefly children and young adults; no sex preference has been noted, and now the studies of Wechsler *et al.* (1946) indicate that the malady is not of so rare occurrence in the Negro as had been believed. Cases are diagnosed the year 'round but most of the epidemics have occurred in the spring and fall. The period of incubation has not yet been accurately determined, the reported extremes being one and twenty-eight days; relapses are not uncommon, occurring in 9 per cent of 556 cases in the epidemic studied by Wechsler *et al.* (1946), and the glandular and hematological changes may persist for

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injection of ho ... time goes on. Both

Halcrow *et al.* ...

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the necessity fo ... e

disease. Kaufman (1944) found the reaction usually remaining positive for two to four months and occasionally persisting as long as one year. Spingarn *et al.* (1944) found cold hemagglutinins in the serum in high titer in a small series of patients. Biopsied lymph nodes do not seem to present a uniform pathological picture, but in Ziegler's (1944) patient, who died of a ruptured spleen in the fourth week of the disease, the microscopic observations sug-

gested that there was hepatitis, nephritis, splenitis and pneumonitis o characteristic and peculiar type; in Allen and Kellner's (1947) autops case there were found cerebral and cardiac lesions, not previously describe Most observers consider the presence in the blood smear of a certain al normal lymphocyte called the "mononucleosis cell" as almost a pathogno monic sign; Contratto (1944) described this cell as follows: "A large mononuclear cell with a pale-staining, rather fragile-looking cytoplasm that curled over on itself and had a large nucleus." Evidence is now accumulating that during an epidemic of infectious mononucleosis there occur many subclinical cases in which neither subjective nor objective symptoms bring the patient under observation, witness the case, in Milne's series (1945), of an apparently healthy young man in whom a ruptured spleen incurred while out skiing led to the diagnosis

This disease was first described by Filatow in 1886 and first definitely envisaged as an acute infectious mononucleosis by Sprunt and Evans in 1920.

THERAPY

In the epidemic of 556 cases, studied by Wechsler *et al.* (1946), all acutely ill patients were treated with bed rest, soft diets, forced fluids, sodium perborate mouthwashes and small doses of aspirin. When jaundice was presen' the patients were placed on the sort of diet that would be employed in acut infectious hepatitis (see Index), in fifteen consecutive cases with concomitant hepatic involvement, Cohn and Lidman (1946) found that the employment of this type of diet much shortened the period of hospitalization.

Infectious mononucleosis is correctly listed among those diseases in which penicillin does not have a specific effect, but Joyce (1946) pointed out the value of this agent in those instances, of frequent occurrence, in which there is a very severe sore throat or tonsillitis, in his experience the response of this complication to penicillin therapy was very gratifying. Wechsler *et al.* (1946) found sulfadiazine unable to produce any spectacular response or to exert any effect on the duration of the disease in the large number of cases in which they tried it Smith and Shaw (1945) employed neoarsphenamine intravenously in six patients suffering from severe throat involvement and felt that speedy and conspicuous benefit was obtained; Story and MacCabe (1946) reported similar results in a single case. Lassen and Thomsen (1940) used convalescent serum with satisfaction, but their series of cases was very small.

Nolan's (1935) list of "don'ts" based on experience in an epidemic of 220 cases is probably still good advice: (a) No heat or hot applications to glands. (b) No hot baths in the acute stage. (c) No rubbing, massaging, or applications in or about the cervical or inguinal glands. (d) No catharsis. (e) When convalescent, no violent exercise involving strenuous stress about the groin or neck. Bernstein (1940) felt that despite the remarkable lack of cross-infection in individuals in close contact with sporadic cases, strict isolation should be effected upon the appearance of multiple infections.

INFLUENZA

This entity is distinguishable from the common cold by the fact that, though its onset is sudden with chilliness, there is invariably an aching all over the body especially in the back and legs, the temperature rises rapidly, *prostration* is marked and progressive, and in the beginning at least the signs of involvement of the upper respiratory tract are minimal. Epistaxis is a common early occurrence, there may be a *short brassy unproductive cough*, but a

infection since the causative virus has not been recovered from the blood of patients; the experimental findings of Henle and Henle (1946) in lower animals suggest, however, that the virus may exert a toxic effect on various organs even though it may be able to propagate only in the respiratory tract. Francis (1943) concluded that, in view of the fact that significant pathological changes *have not been recognized in organs other than those of the respiratory tract*, the disease represents in its pathogenesis a specific injury inflicted by a virus of sharply selective affinities upon a specialized type of cell lining the respiratory tract; according to this authority it seems probable that involvement of the pulmonary tissue, which occurs in only a minority of the patients, is secondary to the destruction of bronchial epithelium in which interstitial swelling, peribronchial infiltration and the outpouring of serous fluid and mononuclear cells represent the major changes. The pathologic findings in the lungs in the case of Parker *et al.* (1946), in which secondary bacterial invasion *had not occurred, consisted of edema, alveolar hemorrhages, fibrin*, and the formation of a hyaline membrane.

Since the incubation period of the disease has been thoroughly established by both accidental and purposeful infection to be only twelve to forty-eight hours, and in view of the fact that the course of the uncomplicated average case is amply described in the term "three day fever," the speed of development of an influenza epidemic seems to be due to the fact that persons still in the incubation stage, those who never have more than a *subclinical infection*, frank cases and convalescing cases all serve as sources of infection. The virus *has been recovered from patients* in each of these stages. But just why the disease at times becomes pandemic and sweeps over the world, at a pace more rapid than mere contact would explain, as the most destructive and most [illegible] maladies remains a riddle. Thorough study of the

has refuted the opinion that influenza

s been shown that the *highest attack*

rate is in the ages below fifteen years and that thereafter a gradual decline in [illegible] mortality was lowest

dence and high case fatality characterizing the intermediate age [illegible]

it should be noted that what has just been said with regard to the age distribution of the disease may be taken to apply to civilized communities *only, for* Smillie (1943) emphasized the fact that in isolated and more primitive communities the great pandemic swept away whole populations irrespective of age.

[illegible] infection. Its name is

s widely spread

influence (*influ-*

entia coeli). Greenwood (1935), the eminent statistician, is convinced that the English Sweats of the sixteenth century were outbreaks of this disease; the correlative occurrence of lethargic states was definitely noted by Fernel at that time. Influenza was common in both the new and old worlds throughout

an attack of the disease does not bestow an immunity of very long duration, though the precise limits of this duration cannot as yet be stated.

Very interesting observations on the etiologic agents in influenza have been made in the years since Smith, Andrewes and Laidlaw (1933), confirmed by Francis (1934), obtained a virus pathogenic for ferrets from the throat washings of influenza patients and demonstrated the production of antibodies against this virus during convalescence. The current etiologic nomenclature is the following (a) "clinical influenza," cases from which virus can not be obtained, (b) "influenza A," cases from which the virus of Smith *et al.* (there are many strains) can be obtained, and (c) "influenza B," cases from which the Lee virus, described by Francis in 1940, can be obtained. Influenza A tends to be a sharp clinical disease with abrupt onset and fever and pronounced constitutional symptoms of three or four days' duration, while influenza B is usually less intense and has a more gradual onset and a shorter duration Both of the viruses are recovered sporadically and influenza of both "A" and "B" types has several times been epidemic in recent decades, but of course it is only conjectural that either of them was the actual causal agent during the 1918 pandemic Shope's (1944) work indicating that the virus of swine influenza which may be a prototype of the human disease, is

THERAPY

In addition to the employment of such symptomatic measures as are discussed in Common Cold, the two clear therapeutic indications in influenza are rest in bed and the employment of chemotherapeutic agents.

Rest in Bed.—It was the observation of all who experienced the pandemic of 1918–1919 that mortality was much higher among those who either would not or could not go to bed at once upon the appearance of symptoms. MacNeal and Parker (1944) stressed the fact that vigorous individuals living in comfort

ity and mortality in the hospital personnel on active duty; they said that troops in rest camps largely escaped while their fellows on heavy duty fell victims to the disease. These observers cited the specific instance of a unit of the A.E.F., located in Dijon, in which strict rest in bed was prescribed by military order [illegible]

the experience was not so fortunate. Immediate and absolute bed rest then is mandatory in the treatment of influenza.

Sulfonamides and Penicillin.—*Since by the very nature of their attacks the* viruses of influenza lay the respiratory tract open to secondary infection with pathogenic bacteria, it would seem the part of wisdom in the present state of our knowledge to employ the chemotherapeutic agents in the attempt to prevent complications. Many of the pneumococcal, staphylococcal and streptococcal complications in recent years have been so fulminating that even intensive therapy with both the sulfonamides and penicillin has failed to save some of the patients, though certainly in most instances the response has been satisfactory. Whether or not these fine new agents can save us from such a disaster as that of 1918, should the organism of those days—virus A or B or some other—again become pandemic is unpredictable.

PROPHYLAXIS

Vaccine Subcutaneously.—*Protection Against Type A Infection.*—During [illegible] United States in the winter [illegible]

carry out a controlled clinical trial of the prophylactic [illegible] and B, [illegible]

sities in different parts of the country, in most instances the men were housed as large groups in dormitories and the proportion of them lost from the study [illegible] different times in the vari- [illegible] each [illegible] ontrol [illegible] e not [illegible] ly, as reported by [illegible] unvaccinated and 2.2 per cent of vaccinated individuals were hospitalized with "typical" influenza. Expressed in another way, 3.2 times as many control persons became ill as did those vaccinated, or in still another way, the vaccine was effective in 75 per cent of instances. Critical evaluation of these figures makes it probable, however, that the protection was even greater than above indicated for the reason that, in a droplet man-to-man infection like influenza, a control group that comes in contact with a population half of which has been protected by vaccination cannot be said to be as fully at risk as the normal population, and therefore it might be expected that the incidence of disease among them would not be as great as in the population outside such a study. That such reasoning is actually valid seems to have been shown by the fact that at the University of Minnesota (Rickard *et al.*, 1945) the attack rate

among individuals in the study group, half of whom had received influenza

trols was 9.06 per cent and 8.58 per cent, respectively, as compared with the 38 per cent and 20 per cent in the comparable units in which no vaccination had occurred, the inference is very strong that the incidence of illness in the controls was influenced by the presence of an equal number of vaccinated persons and that the true effectiveness of vaccination probably greatly exceeds that described by a mere comparison of vaccinated and controls in these studies.

Protection Against Type B Infection.—Francis *et al.* (1946), during an epidemic of influenza B at the University of Michigan, found that the incidence of the disease in an Army unit of 600 men who had been vaccinated was 1.15 per cent while in another service unit of 1100 men who had not been vaccinated it was 9.91 per cent. This certainly indicates a high degree of pro-

studies of Hirst *et al.* (1945), and Hale and McKee (1945), no difference in the incidence of illness was observable in vaccinated and control subjects prior to

vaccine is effective for at least one season and perhaps longer. Indeed, in a fortuitous epidemic that occurred one year after the Army's vaccination study was begun it was found that the highest attack rate among unvaccinated groups was 29.1 per cent whereas the highest rate among vaccinated groups—including those who had actually been vaccinated and also the controls—was

epidemics of influenza A do not occur at intervals of less than two years. The attempts of Henle *et al.* (1946) to increase the efficacy of the vaccine through the use of various adjuvants are interesting but still in the experimental stage. The proposal of other workers to substitute intracutaneous for subcutaneous injections, because of the alleged superiority of the former route, also bears watching.

Dosage.—The routine adult dosage is one injection of 1 cc. Henle *et al.* (1946) found that three weekly injections did not increase the antibody response nor did the inhalation of vaccine in addition to one injection. The striking serological response obtained by Van Gelder *et al.* (1947) to the intracutaneous injection of 0.1 cc. warrants further trial of the method. The suggested dosage for children under twelve years of age is two weekly subcutaneous injections of 0.5 cc. each, but this is probably too high (see Reactions below).

Reactions.—Reactions to the vaccine, which are primarily attributable to the

acter a

Salk a

mately half of the vaccinated individuals had some complaints and that 1 or 2 per cent developed febrile reactions up to 101.5° F. (38.5° C.) within twenty-four hours of inoculation; such symptoms usually lasted no longer than a day. At the site of inoculation, edema, redness and tenderness may develop in about twelve hours and persist for a day or two. Florman *et al.* (1946) were unable to associate an individual's immediate reaction with his subsequent production of antibodies. Grant (1946) found that reaction to 0.5 cc. in children is about the same as in adults when 1 cc. is given but that the use of 1 cc. provoked a reaction that was very severe in some instances.

All of the above applies, as stated, to reactions to the virus itself, but since the vaccines contain a certain amount of egg protein, being prepared from fertile hen's eggs, the egg sensitive individual may experience a severe reaction if vaccinated against influenza. However, Ratner and Untracht (1946) concluded that the use of the vaccine is not dangerous to 99.5 per cent of the general population, which includes all the allergic persons sensitive to proteins other than egg and about 50 per cent of the persons moderately sensitive to egg. With further purification of the vaccine, even this small hazard can be reduced, but at the present time it would still seem advisable, in the opinion of Salk (1947), to exercise caution in the use of influenza vaccine not only with respect to egg sensitivity but also to reduce the dose for children more than would be suggested on the basis of size in comparison with the adult.

Who Should Be Vaccinated.—It seems to me that the indiscriminate vaccination of whole populations in the autumn on the off-chance that influenza may become epidemic during the ensuing season is not justified for two reasons: (a) the diagnosis of influenza by virus isolation or serological procedures has now become a feasible routine laboratory procedure; (b) the group of investigators of influenza is sufficiently large and is so keenly alert that we may expect any increasing activity of the influenza viruses to be detected and announced before wide-spread epidemics can get under way. Routine immunization might perhaps be indicated, however, in individuals who are prone to have each year long bouts of respiratory tract infection and in special groups in which it is particularly desirable to minimize absenteeism during the winter season; college students, employees in certain types of industry and certain Army installations might be examples of the latter sort.

Antiserum Locally.—After the preliminary animal experimentation of numerous workers in several parts of the world, Smorodintsev, in 1940, reported successful immunization in man by the intranasal spraying of serum of highly immunized horses. During an extensive epidemic in Leningrad, 501 volunteers were given the intranasal medication in two doses at fifteen day intervals, 1825 untreated individuals being used as controls; the incidence of infection in the treated cases was 0.4 per cent and in the untreated 8.2 per cent. Francis (1945) stated that the work of the Influenza Commission, the details of which have not yet been reported, did not substantiate the Russian findings. Powell (1944) developed a rabbit antiserum and suggested that after initial influenza cases have appeared in a community about 1 cc. of this antiserum be used *per person* as follows: 0.3 cc. to be sprayed into each nostril, and 0.3 cc. sprayed over the fauces (it is said that the average bulb atomizer delivers about 0.1 cc. at one discharge). In case an

atomizer is not available a medicine dropper can be used but it is not as satisfactory in securing proper distribution of serum. Powell suggested that the antiserum should be used once weekly throughout the duration of the epidemic.

Intramuscular Gamma Globulin.—During a study in which the prophylactic value of gamma globulin against infectious hepatitis was under investigation by Yannet and Deutsch (1946) there occurred an explosive epidemic during which it was apparent that the prophylactic value of gamma globulin against influenza is nil.

Antiseptic Gargles and Sprays.—During the 1918 pandemic the earth trembled and fizzed from the gargling and spraying of the more enlightened portions of its populace in all the hemispheres, but it is not a matter of record that any cases of influenza were thereby prevented. However, MacNeal and Parker (1944) cited some *in vitro* experiments in which they found the virus of influenza inactivated by such mild germicidal agents as the Liquor Antisepticus N.F. VII—and so I suppose that in the next pandemic these agents will be much employed again; certainly no one can deny that a good resounding gargle is a tremendous morale booster.

The Face Mask.—The ordinary gauze mask was much used by hospital personnel during the 1918 pandemic, but recent studies have shown that it is probably not only useless but actually harmful However, there has been developed a new type of mask containing flannel filters which is said to provide protection to the wearer and to the exposed susceptible and to become more efficient with use and laundering, Francis (1943) said that in his opinion the new mask deserves a place in the field of prevention.

Aerosols and Ultraviolet Irradiation.—These matters are discussed under Common Cold

LEISHMANIAL INFECTIONS

(*Kala-Azar or Visceral Leishmaniasis, Oriental Sore or Cutaneous Leishmaniasis, American or Mucocutaneous Leishmaniasis*)

Kala-azar (*dumdum fever*) is common in certain parts of India, in China, Indo-China, the Middle East and Arabia, all around the shores of the Mediterranean (where it occurs principally in young children in the spring and summer), in southern Russia, and in North, Central, East and West Africa. According to Shortt (1945) well marked epidemics of kala-azar have occurred only in northeastern India. Until recently the disease had been considered not to occur in the western hemisphere except for an occasional imported case, but the studies of Penna (1934) in Brazil disclosed a number of infections there and we now know that even earlier reports had revealed the patchy existence of the malady in several countries of South America. At the close of War II leishmaniasis had been diagnosed in the U. S. Army 344 times, but how many of these cases were of the visceral type I do not know. However, kala-azar has since been diagnosed in a few instances in soldiers returned to the American Continent.

Kala-azar is caused by *Leishmania donovani*, a protozoan organism, and everywhere that the disease is encountered indigenously in man it occurs in dogs also, with the possible exception of India. The study of Swaminath, Shortt and Anderson (1942) completed the evidence which incriminated

sandflies of the genus *Phlebotomus* as the vector between man and man. But there are many sandflies and apparently many strains of *L. donovani*; it seems that for each locality there must be the right species of *Phlebotomus* and the right strain of the parasite. And the possibility that infection may rarely occur without the intervention of the fly has not been entirely discarded, for in rare instances viable organisms have been found in the urine, and Forkner and Zia's (1935) finding of viable organisms in the nasal and oral secretions of patients in China has been confirmed by workers in India. The organisms, however they may enter the body, embed themselves in the endothelial cells lining blood and lymph vessels particularly in the spleen, liver and bone marrow, whence they burst into the blood or lymph stream to be engulfed by other endothelial cells or by leukocytes.

The onset is often insidious, though it may be acute. Usually the first complaint is of several bouts of fever with increasing weakness. In one fourth to one third of the cases the fever is of the double-remittent type, *i.e.*, with a rise and fall twice or thrice in the twenty-four hours, in the majority of cases it is of a very irregular sort. Emaciation and, later, anemia (proportionate reduction in red cells and hemoglobin) are pronounced and there is a striking leukopenia with a considerable reduction in polymorphonuclears and increase in mononuclears and lymphocytes. Sometimes the body assumes a dusky hue (*kala-azar:* "black sickness"), the cause of which is not definitely known. Great enlargement of the spleen, and frequently later enlargement of the liver, cause the abdomen to be markedly protuberant, but the absence of splenomegaly or hepatomegaly in an early case does not exclude the diagnosis. In China and Brazil painless adenopathy of the neck has been recorded; Cole (1944) observed enlargement of one or another group of glands, the inguinal and femoral most frequently, in half of his cases in East Africa; in the two very interesting patients of Angevine *et al* (1945), soldiers returned from the Mediterranean area to U S. Army hospitals in England, enlargement of the cervical lymph nodes was the primary and most important symptom Daily rigors are common, though other pronounced symptoms are rare Manson-Bahr (1946) said that outstanding features of the disease are the absence of malaise and the maintenance of good appetite; Cole (1944) remarked these things in the beginning in the majority of his cases also. Diarrhea may be due to the leishmanial infection or to concomitant bacillary, amebic, or flagellate dysentery; both Cole (1944) and Burke (1944) remarked abdominal pain as a not infrequent early symptom. The febrile periods are followed after two to six weeks by afebrile periods, and then further attacks of fever. Obtaining the organisms by hepatic or splenic puncture is sometimes necessary in order to [illegible] bids fair to replace these somewhat [illegible] chances of obtaining a [illegible] th the complement-fixa- [illegible] apparently also had a [illegible] When present in the peripheral blood the leishmania [illegible] may be cultured *in vitro* and established in [illegible] hamster being best suited for the latter purpose. Cole (1944) established quite definitely an incubation period of two to four months for the cases which he studied in East Africa, but presumptive latent periods of as long as two years have been reported In India and Africa and apparently to a lesser extent elsewhere there have been observed rashes which come on when the patient is beginning to recover from visceral leish-

maniasis under the influence of drugs or perhaps some time after the recovery has been completed; leishmania may be found in smears from these skin lesions.

Kala-azar has decimated whole populations in its time. It is said that Indian villagers have burned alive many of its victims, after first stuporizing them with alcohol, in the attempt to stamp out the disease. About 90 per cent of the untreated cases succumb in two months to two years, the immediate cause of death usually being a secondary infection. Cancrum oris, said formerly to occur in about 17 per cent of cases, is nowadays not so frequently seen since a satisfactory form of treatment has been developed; not only the mouth may be involved, for the gangrene may affect such other sites as the cervix of the uterus, the bowel, the lung and the external genitalia. Zia and Forkner (1934) called attention to the occurrence of acute agranulocytosis as a complication of kala-azar in China and speculated upon the possible connection of this with the appearance of cancrum oris, according to Das Gupta and Sen Gupta (1943) agranulocytosis occurs with extreme rarity in the cases in India.

Oriental sore (*Delhi boil*) is a cutaneous leishmanial infection which occurs both endemically and epidemically in many tropical and subtropical regions in both hemispheres. The disease is caused by *L. tropica* and has recently been shown by Russian workers, whose contributions have been thoroughly and critically reviewed by Hoare (1944), to be conveyed by the bite of the sandfly as in the case of kala-azar and to reside in burrowing rodents as reservoir hosts. However, the possibility of direct transmission from person to person still exists since the organisms are recoverable from the lesions; one such case, possibly contracted in this manner in the United States, was reported by Gelber (1942). The lesions, which are usually multiple, are found on exposed parts

which is prevalent in towns and in which the papules persist for months before they ulcerate, the course of the disease being chronic, and the "moist" type, which occurs in the open country and in which the lesions ulcerate in about a week or two and the process tends to run an acute course. It is said that in the moist type the incubation period is one to six weeks whereas in the dry type it may be from two months to a year, that in the moist type lymphangitis occurs commonly while it is rare in the dry type, that few parasites are present in the

which is said to be highly specific, has been developed by the Russians.

American or mucocutaneous leishmaniasis, from the lesions of which *L. braziliensis* is recovered, is prevalent in southern Mexico, Central America and tropical South America (where it is known also as "espundia" and "uta hemeda"). Stewart and Pilcher (1945) described an autochthonous case in Texas and stated the opinion that the rarity of the disease in the United States may be more apparent than real. Shattuck (1938) pointed out that sandflies of the genus *Phlebotomus* have been found in all regions of the Ameri-

cas where leishmaniasis exists with the exception of Peru, for which data were lacking; Pesce and Pardo (1943) more recently supplied evidence that this sandfly occurs in the latter country also. In these mucocutaneous cases the ulcerations involve the ears, nose, mouth and pharynx in very extensive areas of necrosis, the patient often becoming very cachectic and severely disfigured. While ulcerating lesions of the mucosae are occasionally seen in epidemic regions elsewhere in the world, Strong (1942) stated that he had not observed lesions just like those in the American cases anywhere else in the tropics. These mucocutaneous cases, however, comprise only a small proportion of the total number of cases of cutaneous leishmaniasis seen in the Americas.

THERAPY

Pentavalent Antimony Compounds.—Antimony sodium tartrate or antimony potassium tartrate, better known as "tartar emetic," is the classical specific drug in the leishmaniases, but its high toxicity, the fact that it can only be given intravenously, that the time required for the administration of a complete course is very long, and that many cases are completely resistant to it from the

have been produced. These compounds are certainly much less toxic than tartar emetic, they can be given in larger doses, thus reducing the average time required for treatment from two or three months to ten to twenty days; and they are suitable for either intramuscular or intravenous injection. Also, they are apparently much more effective than the earlier drug, there being fewer relapses among those treated with the pentavalent compounds and a considerably lower death rate—4.2 per cent in Napier's series of 167 cases of kala-azar treated with six different pentavalent compounds as compared with 14.4 per cent in his series of 139 tartar-emetic treated cases. Unfortunately, the new drugs are much more expensive than the tartrates and the cutaneous forms of

have the cases in the Sudan, the Mediterranean area and elsewhere.

Solustibosan (Stibanose, Stibatin, Solusurmin, Stibogluconate)—This drug, introduced by the Germans, became unavailable during War II and was therefore widely synthesized elsewhere; hence the multiplicity of names. ... is available in the form of a ... muscularly and *also intra-* ... of the other compounds.

It was early ... in China and India and ev... avarty (1944) more recentl... ut Sen Gupta and Chakravarty (1945), in the same country, were not satisfied with their results until they considerably increased the size of their doses for patients with kala-azar. The dosage which they employed in *their fifty cases, in* forty-eight of which the criteria of immediate clinical cure were fulfilled, ... per pound body ... being ... urse.

The individual dose they felt should not exceed 20 cc. for an adult, 15 cc. for an adolescent, and 10 cc. for a child, it being preferable to commence with a small initial dose to test sensitivity. Their injections were given intramuscularly on consecutive days for ten to twelve doses in most of the cases. In a postscript to their paper they noted that in a period of less than six months five of the forty-eight "cured" cases had relapsed.

Concentrated Solustibosan—Kikuth and Schmidt (1943) reported the preparation of a solustibosan suspension administered intramuscularly to be absorbed from an oil depot. It was said that in children treated with this new preparation in Spain, both local and general tolerance was good when the drug was used in a dose of 1 cc. per kilogram body weight, the full course consisting of five injections at two-day intervals. Remarkably fine results were said to have been achieved. In these Spanish cases a concentrated solustibosan solution five times the original strength was also employed, and it was said that satisfactory results were obtained by administering the drug every twelve hours, a total quantity of 0.4 cc. per kilogram of body weight being given in ten injections in five days. I have seen no record of further trials of this agent since the conclusion of War II.

Urea Stibamine—This drug has been much used in Asia. Rogers said that principally by its use the Assam Government cleared up over 300,000 cases between 1923 and 1935. Lowe (1946) said that it is effective in the vast majority of cases of Indian kala-azar
relatively cheap and fairly safe; he f
that it has to be given intravenously
children whose veins have become blocked by repeated injections. Cole (1944), in East Africa, found this the most valuable of the drugs that he tried. What he called his slow dosage corresponded roughly with the standard dosage of Brahmachari who introduced the drug injections every two to three days, starting with 0.05 gm. and gradually rising; total 2.0 to 2.5 gm. in 15 to 25 injections in twenty to fifty days His more intensive course consisted in giving the patient 14 daily injections of 0 05, 0.1, 0.15, 0.2, etc.; total 2.5 gm.

Neostam.—The recommended intravenous dosage of this agent in Circular Letter No 33, Surgeon General's Office (1943), was 15 doses on alternate days, the first dose of
dose of 4.4 gm. In cases of
used smaller dosage giving
the next 0.1 gm., the third 0 15 gm , and the fourth and all succeeding ones 0.2 gm ; in a few individuals who had frequent untoward reactions the maximum dosage was kept at 0 15 gm The average individual received 1.14 gm. of neostam. Of Ball and Ryan's 221 cases of oriental sore thus treated, 207 were said to have been cured.

Neostibosan—Napier and Mullick (1929), in India, gave a daily intramuscular injection of 0.3 gm. for eight days, the total dose therefore being 2 4 gm Sati (1942) in the Sudan used such dosage intravenously daily or on alternate days for a course of 15 injections. Struthers (1931), in Tsinan, felt that the Chinese patient will not tolerate quite such high individual doses In his series of 87 cases, the initial adult dose was 0.1 gm. intravenously and subsequent doses of 0 2 to 0.3 gm., sometimes daily and sometimes every other day; the average total dose was 2.63 gm. and the average time under treatment was 23.3 days. In children, both intravenous and intra-

muscular injections were given, the initial dose of 0.05 gm. being followed on alternate days by 0.2 gm.; average total dose, 2.1 gm., and the average time under treatment, thirty-two days. Lee and Chu (1935), at the Peiping Union Medical College, found an adequate course for a child was 1.5 to 2.5 gm.; for an adult, 4 to 5 gm. Manson-Bahr's (1946) total dosage to effect a cure was 2.7 to 4.0 gm. This drug does not seem to have become available in the Far East since War II.

Reactions.—The chief reactions when antimony is employed are the following: dizziness, coughing, vomiting, diarrhea, muscle and joint pains, hepatitis (*necessitating immediate cessation of the treatment*), severe headaches and rigors, pronounced slowing of the heart and frightening cessation of the respirations. When using tartar emetic itself, it is said that a somewhat rare drug-induced complication is acute arthritis which usually beneficently influences the course of the primary disease. With the pentavalent antimonials none of these reactions are upon the whole so severe as those seen during the use of tartar emetic, nor do they occur with anything like as great frequency.

Tartar Emetic.—If the expense of a course of treatment with one of the above drugs were to be very markedly reduced there would likely be no point in retaining a description of methods employed with the classical drug, but

TABLE 3.—TARTAR EMETIC DOSAGE IN LEISHMANIASIS.

Time.	Adults.		Children 10 to 15 years.		Children under 10 years	
	Cc. of 2 per cent sol	Gm. of drug*	Cc. of 2 per cent sol	Gm. of drug*	Cc. of 2 per cent sol	Gm. of drug.*
First week 1st injection	1.5	0.03	1.0	0.02	0.5	0.01
2nd injection	2.0	0.04	1.0	0.02	0.5	0.01
3rd injection	2.5	0.05	1.5	0.03	1.0	0.02
Second week 1st injection	3.0	0.06	1.5	0.03	1.0	0.02
2nd injection	3.0	0.06	2.0	0.04	1.5	0.03
3rd injection	3.0	0.06	2.0	0.04	1.5	0.03
Third week 3 injections of	3.5	0.07	2.5	0.05	2.0	0.04
Fourth week 3 injections of	4.0	0.08	3.0	0.06	2.5	0.05
Fifth week 3 injections of	4.5	0.09	3.0	0.06	2.5	0.05
Sixth week 3 injections of	4.5	0.09	3.5	0.07	2.8	0.056
Seventh week 3 injections of	5.0	0.10	3.5	0.07	2.8	0.056
Eighth week 3 injections of	5.0	0.10	3.8	0.076	3.0	0.06
Ninth week 3 injections of	5.5	0.11	3.8	0.076	3.0	0.06
Tenth week 3 injections of	5.5	0.11	3.8	0.076	3.0	0.06
Eleventh week 3 injections of	6.0	0.12	4.0	0.08	3.3	0.066
Twelfth week 3 injections of	6.0	0.12	4.0	0.08	3.3	0.066
Total . .		3.27		2.27	...	1.81

* This column is added by me—H B

since events in the world today seem to be tending to promote *just the opposite effect*, I shall still give a brief outline of the use of tartar emetic. As in the last edition of this book it seems to me that the dosage scheme is best presented in a modification of Young's table (Table 3). This drug must be

given intravenously since its intramuscular injection is very painful and almost invariably causes necrosis. The solution is sterilized before administration. In infants, in whom intravenous therapy is sometimes impossible, administration of tartar emetic is often quite difficult. Saha (1931) reported the successful treatment of 5 cases with rectal injections, introducing 2 cc. of a 0 25 per cent solution after cleansing the rectum with normal saline. The dose was increased 2 cc. in an injection given every second day until 8 cc. had been given; then increasing 1 cc. in an injection every fourth day to 12 cc. in children up to three years; in a girl of ten years he went up to 24 cc. Rectal irritation was not caused. Most authorities consider that both oral and rectal administration usually fail because antimony is absorbed in insufficient quantities, which may cause the infecting organisms to become antimony-resistant or "fast"; however, Chavarria *et al.* (1944) stated that they had used the drug successfully by mouth in a number of cutaneous cases, employing a solution containing 2.5 gm. of the drug in 100 cc. of chloroform water, one drop of this solution containing approximately 1 mg. of tartar emetic. In children treatment was commenced with one drop daily and was increased by a drop every three or four days until the limit of tolerance without diarrhea or vomiting was reached; in adults the initial dose was 5 to 15 drops. Intraperitoneal injection in very dilute solution in physiologic saline was used successfully by Smyly in the cure of a case of kala-azar in an infant, aged six months; however, Caronia (1930), whose experience in the disease was vast, pointed out the at least potential danger of setting up a [illegible]

diamidine stilbene and does not contain antimony, seems to have been found the most potent in the treatment of the leishmaniases. It seems that not only the relatively easily treated cases of kala-azar in India but also the more resistant Mediterranean and Sudan forms of the disease have responded well to this drug. In India, Napier *et al* (1942) treated 100 cases of kala-azar with this agent, the patients being in all stages of the disease. The drug was administered intravenously in a 1 per cent solution in distilled water in ninety-five of the cases and in the remaining five cases intramuscularly, but the latter proved to be very painful. In over ninety of the cases, in which no previous treatment had been given, ten or twelve daily doses were given; in the others, which were resistant cases, up to fifteen injections were given. The dosage finally adopted for adults was an initial dose of 25 mg. followed by doses of 50, 60 or 75 mg. according to reaction, the top dose not exceeding 1 mg. per pound of body weight. In small children the initial dose was 10 mg. up to a slightly higher dose than 1 mg. per pound of body weight, as children tolerated the drug better than adults. After the injection of the agent the blood pressure nearly always showed a marked drop and sometimes the reaction was very alarming to both patient and physician, though it was found that it could be controlled by giving an injection of 0 25 cc. of 1 1000 epinephrine solution just before administration of the drug. Kirk and Henry (1944), in the Sudan, felt that these immediate reactions precluded the use of the intravenous route for outpatients. Ninety-eight of the patients in Napier's series were cured and two died; of the ninety-eight cured cases two relapsed and of these one received a [illegible]

touch, with preservation of sensation of pain, temperature and pressure. Sen Gupta (1943) of Napier's group said that this condition is not dangerous to life and is not progressive and that in most patients there occurred a tendency to slow recovery. This latter author felt that in view of both the immediate and the delayed reaction, and especially since equally good results can be accomplished with the pentavalent antimonials, stilbamidine is not likely to become [illegible]

[illegible]

stale solutions; since the drug is employed at once upon making the solution these severe reactions are no longer seen.

Local Therapy in Cutaneous Leishmaniasis.—In a review of locally employed agents, Avery (1942) included the following: (a) Berberine sulfate injected by means of a tuberculin syringe in 2 per cent solution into the indurated area surrounding the ulcer, about six weekly injections being required for each ulcer in order to infiltrate the whole circumference, 1 cc. of solution usually sufficing; *no further injections are to be made until any inflammatory reaction which occurs has subsided.* Three to six injections have been found sufficient to effect a cure but the treatment is not recommended when there [illegible]

[illegible]

chrysarobin) in ointment form. (d) Injection of a 2 to 5 per cent solution of emetine into the thickened edges and bases of the ulcers, using not more than [illegible]

[illegible]

an anesthetic. Local measures not covered by Avery are the following: atabrine, which Dobrotvorskaya (1941) described as being used in 5 per cent solution injected at several points into the dry type of lesion, both the injections and the 3 per cent solution being employed in treatment of wet lesions; Berberian (1945) failed even with 10 per cent of atabrine; Ball and Ryan (1944) used local injections of 2 per cent neostam solution with good results in 32 of 35 cases; the authors just referred to tried ethyl chloride spray but with very poor results, though freezing with carbon dioxide snow has been reported to be a very satisfactory form of treatment in India; there have been a number of reports of the successful use of roentgen therapy, Bobrov (1942) advocated the withdrawal of 5 to 10 cc. of blood which is soaked up into a cloth and applied to the sore, this being repeated at one to four or five day intervals, the results being reported as very good, but it should be noted that the cases were of the moist type which ordinarily have a comparatively short duration; Gupta and Kahali (1944) reported the successful employment in a small series of [illegible]

[illegible]

PROPHYLAXIS

Sokolova, whose work was critically reviewed by Hoare in 1944, described the results of large-scale vaccinations against cutaneous leishmaniasis in Middle Asia, using material from both the dry and moist types of lesion, the

inoculations being made directly from human lesions or with living cultures. The incubation period varied from a fortnight to a year (average four to five months) while the infection lasted from two to seventeen months (average six to nine months). The total number of persons vaccinated was 1522 of whom 1107 were followed up; the vaccination was successful in 73.8 per cent, best results being obtained with cultures of parasites from sores of the moist variety. The effectiveness of this type of "vaccination" in protecting against new infection is shown in the following figures: among 772 successfully vaccinated persons only 6.3 per cent subsequently contracted the natural disease which in unsuccessfully vaccinated persons natural infections were acquired by 29.3 per cent, these figures to be compared with the incidence of 63.0 per cent in the nonvaccinated population. It became apparent in these studies that the development of immunity as the result of vaccination is a slow and gradual process requiring about a year, thus explaining the susceptibility to superinfection in a certain proportion of the vaccinated persons. Successful vaccination upon a somewhat smaller scale was also reported by Katzenellenbo-- (1944) in Palestine.

LEPROSY

Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever are five major infectious diseases that are not given consideration in this book for the reason that the problems they pose lie nowadays almost entirely within the province of public health authorities or other specialists of great experience.

LEPTOSPIROSIS

(*Weil's Disease, Spirochetal Jaundice*)

This is an acute infectious disease caused in the vast majority of instances by *Leptospira icterohaemorrhagiae*. Onset is usually abrupt with vomiting, headache, fever, muscular pains, especially in the calves of the legs and the abdominal wall, and great prostration, sometimes there is initial chill or chilliness, transient stiffness of the neck, labial herpes, hiccup and cough; conjunctival injection is often present. There is leukocytosis of high degree, though sometimes this sign does not appear until a few days after the onset of the attack. Nosebleed, purpura, petechial and subconjunctival hemorrhages, bleeding mucous membranes, hematemesis and melena evidence a probable local toxic effect of the spirochete on the capillary walls. The urine early contains bile and may show all the evidences of acute toxic nephritic or nephrotic changes. In about half the cases the temperature falls in three or four days to a week and the patient goes on to recovery, but in the other cases jaundice appears at about the time the temperature falls and the liver becomes tender and swollen; the spleen may be palpable. In these severely ill patients there is an increase in the hemorrhagic tendency and often renal failure occurs; delirium or semi-coma and a rash often appear, but the temperature usually remains low. In the United States, Stiles *et al.* (1940), confirming earlier continental observations, recorded two cases in which there occurred evidences of severe renal damage without jaundice. Bruno *et al.*

(1943) said that symptoms and findings referable to the heart were not uncommon in their experience, and a similar observation was made by Senekjie (1944). On the Continent and in England (Lescher, 1944, Robertson, 1946), a meningeal form of the disease is recognized and the statement of Ashe *et al.* (1941) that it occurs in our country also was corroborated by the findings of Clapper and Myers (1943) and Senekjie (1944). Strong (1942) stated that in Japan the mortality rate is as high as 48 per cent while in Europe it ranges from 4 to 32 per cent, in Senekjie's (1944) thirty cases in the United States the mortality rate was 16.3 per cent. In those surviving the severe attack defervescence usually begins at the end of the second week, but there are sometimes one or more mild relapses and convalescence is often very protracted. Leptospiral vegetative endocarditis, iridocyclitis (and much more rarely optic neuritis) have been recorded as late complications.

The causative organism is present in the blood up to the seventh day and appears thereafter in the urine where it persists for a long time after recovery. It seems that darkfield examinations for *L. icterohaemorrhagiae* are very misleading. The blood also gives a positive agglutination reaction after nine or ten days; if the titer is high after fourteen days it is considered diagnostic. Ashe *et al* (1941) said that a negative reaction after thirty days rules out Weil's disease. In Senekjie's (1944) opinion, based upon positive reactions in 80 per cent of his cases, the titer must be at least 1:300 with a steady rise in order to be of diagnostic significance, but Tiffany and Martorana (1942) believed that a titer of 1:1000 is indicative of present or recent infection Another test consists in injecting blood and urinary sediment from the patient into a young guinea pig which will become febrile in a few days and is said to yield the organism from its aspirated peritoneal fluid before death; in connection with this test Murgatroyd (1943) suggested that alkalis be given the patient in order to neutralize the urine before taking a specimen since the organisms soon die in acid urine. Sheldon (1945) suggested biopsy of the muscles of the calf as a useful diagnostic measure since rather typical lesions were found in this way in his seven cases.

L. icterohaemorrhagiae is found in wild rats the world over, and it is significant that most recorded sporadic or epidemic cases have occurred in individuals who have passed some time in wet, rat-infested places, such as military trenches and civilian excavations, natural swimming pools, mines, sewers, dirty canals, rice-paddies, dank fish-handling establishments and slaughterhouses, or hav
break was presumably
novitiate. Insects have
or slime being infected
rhagiae will live in stagnant water for three weeks. The organism has been found in the urine of dogs, cats, foxes, field mice, pigs and horses; less often mink, mongooses, bats, bandicoots, voles, calves and poultry—some of these organisms, having given rise to disease in man not precisely like classical Weil's disease, have been distinguished by different names (*L. bovis* from calves, *L. grippo-typhosa* and *L. sejroe* from small field rodents, and *L. pomona* from swine). Laboratory workers have become infected from albino rats that had been infected by wild rodents; guinea pigs are occasionally, but white mice more often, carriers of the disease. The organism has been passed from dogs to man in a number of instances, but passage from dog to dog has not been proved, which indicates that the dog likely obtains

it from the carcass of one of the other carrier animals; but there is a serious infectious jaundice in dogs (dog typhus or Stuttgart disease), which is caused by *L. canicola*; man has been infected by contact with these dogs, but this canine organism does not occur in rats Man-to-man infection with *L. icterohaemorrhagiae* is apparently very rare though a case has been reported of transmission by copulation and it seems that intrauterine infection of the fetus can occur.

Weil's disease occurs all over the world and in some areas the incidence is rather high; that we will find many more cases than hitherto suspected in the United States was indicated by the fact that thirty cases were diagnosed in the Charity Hospital of New Orleans from September, 1939, to February, 1944 (Senekjie). Males preponderate among the patients and children are rarely affected; most cases occur during the summer In an epidemic among laborers in the Andamans, the onset of the first case was six days after the beginning of work in a leptospira-infested swamp, Schüffner (1934) found an average incubation period of 10 3 days in 452 cases in Holland, the range being between four and nineteen days

Weil first described this disease in 1886, and Inada and Ido discovered the causative organism in 1914

THERAPY

Penicillin has been used by a number of physicians in a single case or in series of four to six cases, sometimes with favorable but more often unfavorable results. Robertson (1946) tried it in four cases, in the three in which it was used rather late in the course of the illness there was no effect attrib[illegible]table to its employment, but in the one case in which it was used early i[illegible] appeared that a good result was obtained The largest series of cases I have seen recorded is that of Bulmer (1945), who treated sixteen cases, the consensus of himself and the other officers who observed these cases was that (a) penicillin in large dosage appeared to effect a reduction in the duration of fever and the number of relapses, (b) it did not influence the degree and duration of the cholaemia or the rate of disappearance of icterus from the skin or [illegible]ile from the urine, (c) it did not influence the degree of nitrogen retention or the rate of disappearance of albuminuria, (d) it did give rise to the definite clinical impression that dramatic improvement was effected within thirty-six hours. Upon the whole, it would appear that if the profession were to become fully alert in the matter of leptospirosis so that at least presumptive diagnoses would be made early in the course of the disease, penicillin might be expected to be very helpful

One would be hopeful of the intravenous arsenicals here, but they have failed; indeed, some cases have been made worse by their use, probably because of the state of the liver The antimonial drugs have also failed Studies with experimental animals have indicated that bismuth might have real value, but years have passed and there has still been no thorough trial in the human The sulfonamides have been tried without success.

An allegedly potent antiserum prepared by raising the agglutinating titer of horse serum was originated in Japan and is said to have been used successfully both there and in Europe. Tokuyama (1940) gave 40 cc. intravenously every twenty-four hours according to Inada and Ido's ori[illegible] instructions in a small series of cases in Hawaii, but it is not [illegible] the effect was very great; D'Silva (1942) gave 40 to 60 [illegible] [illegible]ith disappoint-

ing results; Hutchison *et al.* (1946) used it in three cases with no obvious beneficial effects. Keay (1938) successfully employed transfusions from a convalescent donor and obtained "spectacular" results in his two cases. Ashe *et al.* (1941) also transfused convalescent blood in a single case—the patient had been anuric for thirty
antibodies, previousl
the blood. Patterson
convalescent blood in the one case in which he used it; however, one should point out that 250 cc. of convalescent whole blood were given in the fourth week of the disease to one of Senekjie's (1944) patients without appreciable results

Since in most cases the treatment must obviously be symptomatic, Senekjie (1944) advised that the patient be given high carbohydrate, high protein and high vitamin diets to support the liver and that calcium gluconate be administered parenterally. Fluids must be pushed. Robertson (1946) treated two out of three cases of anuria successfully with high spinal anesthesia up to the level of D7; Williams (1947) also succeeded in his case, the assumption being that anuria in these instances is due to diminution of glomerular blood flow as a result of vascular spasm.

PROPHYLAXIS

In Japan, large-scale employment of horse antiserum has been made in prophylaxis, but Walch-Sorgdrager (1939) said that this is not routinely done in Holland even in the case of an individual who has fallen into one of the highly infected canals; only one in seventy-five such persons contracts the disease and to such a one the serum is administered upon the first appearance of symptoms. Schüffner (1941) used prophylactic injections of vaccine in twenty-one individuals who had been exposed through handling a colony of infected rats, the vaccine was made from rich cultures of the organism, subjected twice for thirty minutes to 70°C. and injected intravenously, first 1 cc and on the eighth day 2 5 to 3 cc. (a few reactions of an allergic nature he felt could have been avoided if the second injections had been given on the sixth day). Das Gupta (1942) also effected active immunization in man by the use of leptospiral vaccine
had better be disinfected and disposed of, and
nd Sawers
ading the
disease; there would likely be no point in keeping the patient in hospital until the urine is free from organisms.

LISTERELLOSIS

This is a sporadic infectious disease of the central nervous system, of world-wide distribution but of very rare occurrence The causative organism,

entry in the human being is obscure, though Julianelle
tration through the gastro-intestinal tract is most likely. The usual clinical

picture is that of sepsis with severe meningoencephalitic involvement, with the organism recoverable from the cerebrospinal fluid. Twenty-three cases have been definitely and thirteen cases probably diagnosed in man; the mortality, excluding three cases recently treated with sulfonamides, has been approximately 70 per cent, death usually occurring within a week.

THERAPY

Kaplan (1945) wrote that three patients had recently been successfully treated with sulfonamides, but I have not seen these reports.

MALARIA

Malaria is an infectious disease caused by plasmodia conveyed from infected to healthy persons by the bite of the females of certain mosquitoes of the subfamily *Anophelinae*, in whose body the organism passes a part of its life cycle. When the mosquito bites a malaria-infected individual she takes into her stomach two forms of plasmodium, trophozoites and gametocytes, the latter being called "crescents" in the case of falciparum infection. The trophozoites (which may be in any stage of growth from the earliest ring form up to full-grown schizonts ready to segment) are destroyed just as any other food substance, but the gametocytes, which are sexual forms, survive and fertilize and eventually give rise to active sporozoites, which make their way into the salivary glands and are then injected into the blood of an individual subsequently bitten by the mosquito. In certain of the bird malarias it has been found that these injected sporozoites enter and inhabit the lymphoid-macrophage system and endothelial cells and occasionally heterophiles and eosinophiles, and that entrance into the erythrocytes is only made by forms thereafter erupting from these tissue cells. Such an exoerythrocytic (cryptozoic) stage has not yet been unequivocally demonstrated in man, and therefore at present we can only say that after a time, having undergone a metamorphosis somewhere, the sporozoites injected by the mosquito reappear as plasmodia in the red blood cells, where they mature and finally erupt into the blood stream as a shower of young merozoites that enter fresh red blood corpuscles and repeat the cycle, thus giving rise to the symptoms of the disease. Some of the merozoites, however, will have matured in red blood corpuscles not as schizonts but as gametocytes, sexual forms which cause no symptoms and finally die if not taken out of the blood again by a mosquito.

The accepted species of human plasmodia are *Plasmodium vivax*, *P. malariae*, *P. falciparum* and *P. ovale*. The last-named species is thought of as occurring principally in West and Central Africa, and since these are the regions inhabited by the great apes it has been looked upon by some observers as a form of monkey malaria just becoming adapted to man; however, it has recently been reported from China, Colombia, Venezuela and the Philippines and possibly in the course of time it will be differentiated elsewhere. Ovale infection is usually extremely mild and will not be the subject of special description in this book. *P. perniciosum*, *P. tenue*, and *P. aethiopicum*, each of which was at one time proposed as a special species, are all now generally accepted as local variants of *P. falciparum*, the specificity of *P. wilsoni* is yet to be demonstrated.

longer in quartan than in vivax attacks, the quartan paroxysm is nevert less definitely more exhausting to the patient. The spleen does not enlar to the extent it does in vivax malaria nor does the anemia develop as rapidl but in quartan malaria the signs and symptoms of nephrosis develop muc more frequently than they do in vivax malaria. It is said that untreate quartan infection may continue clinically active for as long as nine months when terminated by specifio therapy, quartan relapses about as does vivax in the early months but it is notorious for its long duration—at least one relapse after thirty years has been recorded by a reputable malariologist The immediate prognosis in an acute attack is about the same as in the case of vivax infection.

In falciparum malaria (*P. falciparum*) the prodromal symptoms may be about as in the other two types of malaria, but in some instances there are no prodromata at all and the patient will suddenly go into a paroxysm, perhaps even directly into coma; in fact, Kean and Smith (1944) reported that of 100 patients dying of falciparum malaria in the Gorgas Hospital in the Canal Zone over a period of years, the duration of symptoms before hospitalization varied from four and one-half hours to twenty-one days and that twenty-three patients had symptoms for not more than one day before hospitalization and yet they died In most instances, however, the usual paroxysm occurs in falciparum as in the other forms of malaria though the rigor is often not very pronounced, vomiting occurs very frequently at the end of the cold stage and there is often abdominal pain and diarrhea. Perhaps the most outstanding feature of falciparum infection is the long duration of the fever and the nonintermittent type of the fever curve; indeed, the febrile course is of a very irregular sort because of the appearance and disappearance of cycles so that th [illegible] remittent and continuous periods combine in [illegible] ment of paroxysms. Kitc [illegible] basic tertian cycle, but [illegible] of the tendency of falci [illegible] postpone in relation to the time of the previo [illegible] en does not ordinarily enlarge as much in the primary falciparum attack as it does in the first vivax attack but the degree of anemia is usually much greater, indeed, in a week of illness the patient may lose more than 2,000,000 erythrocytes per cu. mm. and 5 gm. of hemoglobin per 100 cc. of blood. Most feared of all, however, are the "pernicious" symptoms in this type of malaria During the middle of War II when the Allied armies came to be much involved in malarious regions around the world, many papers appeared in which these pernicious types were described rather breathlessly and with wonderment because they were being seen for the first time by the recording observers. However, there is nothing new about all this, since tropical practitioners have been long aware of the fact that not only may falciparum malaria involve in sledgehammer fashion many systems of the body, but also that many of these seizures will tax to the utmost the differential diagnostic skill of the most astute physician. The symptoms may run the amut from those of the so-called "algid" type, in which the patient collapses uddenly and is found cold, practically pulseless and unconscious, through the rious gastro-intestinal, respiratory and other types. The range of what may expected I think was very comprehensively presented by Kitchen (1941), ose listing follows herewith: (a) *Nervous system:* hemiplegia, paraplegia, alized paralysis, epileptiform seizures, neuritis, headache, irritability, restness, delirium, convulsions, coma, tremors, ataxia, speech changes, aphasia,

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changes, and so on) may take place in the liver, spleen and bone marrow, the other parenchymal organs are kept sufficiently clear of parasites that damage is not done and the patient does not die. In falciparum malaria with some one of these pernicious complications, however, the increase in the rate of production of the parasites is apparently so great that vast accumulations of them remain unfiltered out by the reticuloendothelial system and we have the relatively grossly recognizable feature of plugging of the capillaries in any part of the body, which will account for even the most bizarre of the symptoms. However, Viswanathan (1944) concluded that the primary lesion in cerebral malaria is damage by malarial toxins to the capillary endothelial wall with secondary thrombus formation and accumulation of red cells and pigment, the presence of actual parasites in the blood being immaterial; he was able to cite three fatal cases in which no parasites were found in the cerebral capillaries

high as 25 per cent and that in cerebral cases in which the patient is in coma and having convulsions it may rise to 80 per cent. Of course with early diagnosis and adequate treatment these figures are much lowered; in Einhorn and Tomlinson's (1946) series of 493 cases of children with falciparum malaria in Panama, the mortality was only 2 4 per cent. The falciparum paroxysm, when it can be clearly distinguished, may last anywhere from six to thirty-six hours, but the total duration of the irregular and asymmetrical fever curve during an untreated primary attack is not likely to exceed six weeks, which is a much shorter period than characterizes either of the other forms Furthermore, falciparum infections probably do not persist in a latent form for more than a year, and as a matter of fact most of the relapses have occurred within six months. Nagley's (1945) report of a presumptive relapse after thirteen years is certainly a curiosity.

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dromes of nephritis and nephrosis (albuminuria, casts), hemoglobinuria, hematuria, orchitis and oophoritis. (f) *Other systems:* involvement of special senses as hearing, sight (optic neuritis, retinal hemorrhage) and mastitis. Cannon (1941) expressed the consensus in explanation of these protean manifestations in saying that in benign malaria the reticuloendothelial cells in the liver, spleen and bone marrow can phagocytose parasitized erythrocytes at a sufficiently rapid rate that, while pathologic complications (infarcts, toxic changes, and so on) may take place in the liver, spleen and bone marrow, the other parenchymal organs are kept sufficiently clear of parasites that damage is not done and the patient does not die. In falciparum malaria with some one of these pernicious complications, however, the increase in the rate of production of the parasites is apparently so great that vast accumulations of them remain unfiltered out by the reticuloendothelial system and we have the relatively grossly recognizable feature of plugging of the capillaries in any part of the body, which will account for even the most bizarre of the symptoms However, Viswanathan (1944) concluded that the primary lesion in cerebral malaria is damage by malarial toxins to the capillary endothelial wall with secondary thrombus formation and accumulation of red cells and pigment, the presence of actual parasites in the blood being immaterial; he was able to cite three fatal cases in which no parasites were found in the cerebral capillaries.

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In most transfusion malarias reported in the United States the donors were in a latent period of quartan infection acquired years before in the Mediterranean countries from which they had emigrated. For example, Rubenstein *et al.* (1945) showed that of the twelve cases reported in Massachusetts since 1929, nine (possibly ten) were caused by P. *malariae* latent in five of the donors for from twelve to twenty-seven years

The number of such individuals is large for the number of cases that occurred in the Armed Forces probably approximated 1,000,000; furthermore, some soldiers who come home ostensibly malaria-free will develop first evidences of infection a long time after their return (see discussion of the incubation period further on). Lundy (1946) suggested the following rules to be applied at the Mayo Clinic: Rule 1. If the prospective donor has been in a malarious area and has had an attack of malaria, he should not be used as a donor for at least two years after leaving the zone, provided that he discontinued suppressive treatment then and has not had any recurrences of malaria for at least two years previous to his donation Before donation a thick smear should be examined and found to be negative Rule 2. If the prospective donor was in a malarious area and has not had an attack of malaria for the past year and has not taken any suppressive treatment, he may be used provided a thick smear does not reveal any parasites. The history of undiagnosed fever or a questionable history should cause the application of Rule 1. Will malarious blood lose infectiousness through storage? Hutton and Shute (1939) answered that all species of plasmodia survive for weeks at usual storage temperatures McClure and Lam (1945) reported two patients infected with blood refrigerated for five days; however, Antschelewitsch (1937) failed to transmit the disease in all eleven instances in which he stored known malarious blood more than eight days. In the event it is foreseen that a suspected donor must be used, it is possible that if he takes one of the newer drugs for as long as is feasible before giving his blood, transmission of his latent infection may be prevented. When vivax malaria has been transmitted through blood transfusion it does not relapse but both falciparum and quartan do. Malaria is also transmitted by the lower class of drug addicts through the common use of an apparatus for the administration of the opiate intravenously. Most and Jolliffe (1940) reported more than 200 cases of the falciparum type admitted to Bellevue Hospital in the period 1933–1940 Black (1940) submitted presumptive evidence of the transmission of malaria during the routine administration of neoarsphenamine by the gravity method in a syphilis clinic.

Malaria in infants and in children up to three years of age presents a different clinical picture from that seen in the adult Periodicity in subjective and objective symptoms is absent more often than it is present, and fever is more often remittent, irregularly intermittent, or absent, than regularly intermittent and, of course, a convulsion often replaces a chill. Enlargement of the spleen fails to occur in perhaps 30 per cent of cases in infancy. Numerous cases of fetal infection through the placenta are on record, but the consensus is that such infections cannot occur if the placenta is normal, though of course it is conceivable that the malaria itself may induce such pathological changes in the placenta as to make it permeable to the parasites.

As an untreated patient continues to experience relapses or reinfection the enlarged spleen may extend to the pelvis and will become fibrotic and firm, this "hard" spleen often persisting long after the patient has ceased to have acute attacks of malaria. It is recognized also that numerous more or less permanent residuals of a neuropsychiatric nature are chargeable against falciparum malaria in which delayed diagnosis or faulty therapy has permitted the occurrence of embolic or hemorrhagic damage during a cerebral type of paroxysm. Numerous other things, in addition to the classical "cachexia" with its emaciation, weakness, anemia, anorexia, diarrhea, menstrual disturbances, mental depression, etc., are ascribed to chronic

fore, just preceding the paroxysm the count of the organisms in the peripheral blood will be very much lower than at other times.

It is generally said that the average incubation period of malaria is ten days but perhaps fourteen would be more accurate. In the temperate zones some of the vivax infections seen in the spring and early summer are relapses but many of them are primary attacks resulting from the organism's ability to hibernate in the body during the winter (the infecting bite having occurred in the preceding autumn), in midsummer and autumn both primary attacks and relapses occur. In these zones most falciparum cases are seen in the late summer and early fall. In the tropical zone infections with any of the parasites ordinarily give rise to attacks at once after the usual incubation period, but even in these torrid lands there is a seasonal periodicity of malaria not always easy to account for; the interested reader is referred to Colonel Gill's (1938) exhaustive and fascinating book on the subject. As a matter of fact, in the temperate zones we must learn to recognize the possibility of the occurrence of malaria in anyone who has ever been exposed to infection. Specifically this sort of thing may happen: an individual returning from the tropics in the winter may come down with an illness the following spring His story to his physician would be that he had had severe malaria in the preceding summer and had experienced one or two relapses and had then completely recovered and was declared cured. The physician might then search exclusively for other diseases than malaria in his patient. This could easily cause a diagnosis to be missed, for Boyd and Kitchen (1938) showed that it is not unusual for a person multiply infected to experience falciparum attacks in the summer or fall and then have a vivax attack in the succeeding spring, Mayne and Young (1938) also showed that in mixed infections with vivax and quartan organisms one or the other of the species always predominates in much the same way. Then, too, we must also become aware of the fact that unusually long incubation periods are not infrequently encountered; 1.7 per cent of 2579 patients at the Marine Barracks, Klamath Falls, Ore , did not experience their primary attack until they had been out of the endemic area for more than a year.

Malaria is the most important disease, infectious or non-infectious, with which mankind has to contend, for it kills more people than any other and seriously curtails the socio-economic efficiency of the masses who are still unable to obtain adequate treatment. Experience in War II awakened the lay public to the fact, already known to most physicians, that malaria still reigns supreme throughout most of the tropical and many of the subtropical regions of the world. In the United States the disease has held sway in its time from the Gulf of Mexico to the Great Lakes (including extension well up into Canada) and from the Atlantic Seaboard to well past the Mississippi River; indeed, with the beginning of extensive agriculture on the West Coast and the incursion a few years later of successive migratory waves and the hordes seeking gold in 1849, malaria became established first epidemically and then endemically along our Pacific Seaboard But the recession from the Upper Mississippi Valley, where the disease had been deeply entrenched, began, according to Ackerknecht (1945) in the 1860's; the disease has now nearly disappeared from practically all the states north of the Ohio River, except for limited regions of vivax endemicity, and even the more highly endemic regions in the South have materially shrunken in the last few decades (Faust *et al*, 1946). In late 1944, when great numbers of malaria-infected soldiers were returning to the Con-

tinental United States, I ventured the opinion that at least here in my home state of Wisconsin the likelihood of malaria again becoming endemic was extremely remote though it seemed possible that we would for a time have small explosive epidemics about foci of infection; but it seems that I was wrong for not only did these small epidemics fail to materialize in Wisconsin but they did not occur elsewhere either, and now it is unlikely that they ever will since the decline in imported cases in the Armed Forces has been very steady since mid-1945. *In fact, under the inspiration of Dr. L L. Williams, Jr., Mountin* (1944) of the U.S.P.H.S. proposed a program for the eradication of malaria from the Continental United States, and I believe it is the consensus of malariologists that such eradication is entirely feasible despite the influx of cases contracted abroad during the war.

Malaria was well known to the ancients. Garrison, quoting Blake, said that the theory of its conveyance by mosquitoes was indicated even in the Sanskrit Susruta, while another author holds it responsible for the vacillation of the Greeks before Troy Williams (1941) said that a Chinese manuscript of the third century B C. advised the traveler entering regions where chang-chi ("malicious air") prevailed to make arrangements for the remarriage of his widow. Hippocrates gave classical descriptions of malaria. It has been learnedly held that this ailment, by driving the population cityward, was a pronounced causal force in the final decline of the Greek civilization, and that the later Roman Empire must sooner have succumbed to attacks from the north had not the barbarian hordes been decimated by the ague. The Middle Ages knew its ravages, too, while in many a military campaign of the eighteenth and nineteenth centuries more men fell victim to chills and fever than succumbed to shot and shell The French failure to construct the Panama Canal was due in large part to this disease, and in War I malaria was one of the chief causes of disability at troop concentration areas within the "malaria zone";

book.

Laveran discovered the causative organism of malaria in 1880 but the modern sanitarian's attack upon the disease did not begin until after Ross, Bignami and Grassi and others in 1898 had incriminated *Anopheles* mosquitoes as the vector.

THERAPY OF VIVAX (BENIGN TERTIAN) MALARIA

tissue (exoerythrocytic, cryptozoic) phase of the infection that is responsible for the relapses through more or less periodic outpourings of organisms into

much longer period of time than is the case in the vivax malaria previously familiar to us here in the United States But cure is ultimately achieved as humoral immunity rises and the eruptions from the tissues diminish and finally

cease. Usually the patient's life has not been seriously endangered by his malady, but he has often been quite ill during the paroxysms, sometimes the not entirely asymptomatic intervals between attacks leave him in a low and dispirited state, and he usually loses a considerable amount of time from his occupation while his malaria is "burning itself out." The rational objectives of therapy are therefore quite simple: treat each attack vigorously in order to terminate it as quickly as possible, look to the patient's welfare between attacks, and employ all the means at one's disposal to reduce the total number of these attacks Fortunately, as a result of the fine experience of malaria that was had both in the laboratories and in the field during War II, we are now in a much better position to treat the disease than we were a few years ago.

Therapeutic Superiority of Chloroquine (Aralen) to Quinacrine (Mepacrine, Atabrine) and Quinine.—Chloroquine was patented in Germany in 1939 under the name of resochin but it was not extensively studied there; its full investigation and development as an antimalarial agent took place in the United States during the recent war. Loeb *et al.* (1946), constituting the Board for Coordination of Malarial Studies, have published a statement of the antimalarial properties, pharmacology and toxicology of this new agent, but the most exhaustive clinical comparison of it with quinacrine and quinine was [illegible] Moore Gen-

[illegible]

the onset of the current attack, and the drugs were compared on the basis of their efficacy in controlling parasitemia, fever and other symptoms and in affecting the interval prior to relapse. The observations in more than 1000 acute attacks were analyzed.

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[illegible]

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Control of Fever.—The superiority of chloroquine to quinacrine or quinine in promptly controlling fever was evident in infections of both origins regardless of the initial parasite density, and in the Pacific infections regardless of whether the attack was the first or a relapse at any stage of the disease. With chloroquine only 2.1 per cent of the patients had fever the day after treatment was begun or subsequently, while this figure for the quinacrine group was 8.0 per cent and for the quinine group 8.7 per cent.

Control of Other Symptoms.—The drugs could not be so easily compared upon a statistical basis in connection with the control of other symptoms, but certain very definite impressions were obtained in the study. For example, chloroquine was felt to be at least as good as quinacrine or quinine in the control of all symptoms and superior to one or the other in the control of some symptoms. Headache and backache were relieved more rapidly with chloroquine or quinine than with quinacrine. Quinine was more effective than quinacrine in the control of generalized aching but not significantly better than chloroquine. Weakness, dizziness and light-headedness disappeared more rapidly with chloroquine or quinacrine than with quinine. Nausea persisted longer in patients treated with quinine than in those treated with the other two drugs, while the duration of vomiting, abdominal pain and abdominal tenderness was essentially the same with all three.

Effect on the Interval Prior to Relapse.—During the first month after treatment, none of the chloroquine-treated cases had relapsed, 9 per cent of the quinacrine cases had relapsed and 54 per cent of the quinine cases. At forty days, relapses began to appear in the chloroquine group, but they occurred in less than 1 per cent of the patients, while 28 per cent of the quinacrine group and 67 per cent of the quinine group had relapsed at that time. At fifty days, 11 per cent of the chloroquine patients had relapsed, 40 per cent of the quinacrine and 72 per cent of the quinine. At 120 days, 70 per cent of the chloroquine cases, 80 per cent of the quinacrine and 85 per cent of the quinine cases had relapsed. Thus it is evident that while neither of the three drugs materially influenced the ultimate rate of relapse following treatment of the acute attack, with chloroquine the average interval before relapse after treatment was about two weeks longer than with quinacrine and at least five weeks longer than with quinine.

Continuing Freedom from Relapses.—Most *et al.* (1946), in the study above summarized, were unable to study the effects of these drugs in keeping the patient free from relapses when administered in small dosage over a long period of time after the cure of the acute attack, but Loeb *et al.* (1946), reporting as the Board for Coordination of Malarial Studies, stated that after arrest of the acute attack freedom from further attacks may be assured by administering chloroquine once weekly in suppressive doses (see Suppressive Treatment below), though admittedly insufficient experience has been had with this agent as yet to indicate whether "cure" can be accomplished with its administration in this way over a reasonable length of time. Baker (1946) felt that the continuous suppressive administration of quinacrine for eighteen months after controlling the acute attack would cure the disease; his study did not indicate precisely how much one might hope to shorten that period but he did learn that six months administration was not long enough.

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Control of Parasitemia.—Starting with parasites present in the blood in all cases, negative smears were obtained within twenty-four hours after the first dose of drug in 38 per cent of the chloroquine-treated patients, 26 per cent of the quinacrine-treated patients, and 9 per cent of the quinine-treated patients. At forty-eight hours the percentages of patients with negative smears in the three groups were 86 per cent for chloroquine, 77 per cent for quinacrine, and 45 per cent for quinine. At seventy-two hours, while 96 per cent of the patients treated with either chloroquine or quinacrine had negative smears only 77 per cent of the patients treated with quinine were parasite-free. At ninety-six hours practically all patients in the three groups were negative although a few treated with quinine continued to have parasitemia for as long as 132 hours. It was the opinion of the observers that all the differences between the drugs observed in the percentage of negative smears at twenty-four and forty-eight hours were statistically significant and that at seventy-two hours the difference between quinine and either chloroquine or quinacrine was significant, though at this time there was no significant difference between chloroquine and quinacrine. Since the rate of parasite clearance with any drug, particularly during the first forty-eight hours of treatment of the acute attack of vivax malaria, is grossly related to the initial parasite density, this fact was taken into account in the study of Most *et al* and the initial parasite densities equalized throughout the three groups of cases so that the differences in the results obtained with the three drugs are actual and not merely apparent. The chloroquine superiority was manifested in cases of both Mediterranean and Pacific

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Summary.—Summarizing the above information, it seems that chloroquine is superior to quinacrine and both are superior to quinine in eliminating parasitemia, reducing fever, and controlling the other symptoms of the acute attack of vivax malaria whether of Pacific or Mediterranean origin. Since both these strains of malaria are more resistant to treatment than the strains indigenous in the United States, it will probably follow that the control of our own native malaria will be even easier to accomplish with chloroquine than is the case with these imported malarias. An additional very important advantage of chloroquine is the much longer interval before relapse when it is used instead of either of the other drugs.

Chloroquine (Aralen, SN-7618) Dosage and Toxicity.—*Dosage*—Chloroquine is used in the form of its diphosphate salt, which is commercially available under the proprietary name of aralen diphosphate; it is supplied in 4 grain (0.25 gm.) tablets. In all of the clinical studies with this drug, such as that of Most *et al.* discussed above, this diphosphate salt was used but dosage was calculated in terms of chloroquine base. Currently recommended dosage in terms of aralen diphosphate as available commercially is 4 tablets (1 gm.) to be administered when the diagnosis of malaria is established by a positive blood smear, 2 tablets [illegible]
taken as a single dose on each of [illegible]
of 10 tablets (2 5 gm) taken in [illegible]
treatment of the acute attack. As previously stated above, the suppressive dosage of 2 tablets (0 5 gm.), administered on exactly the same day each week, will maintain the patient free from relapses after the acute attack is controlled. A chloroquine dosage scale for children has not yet been developed.

Toxicity—In the experience of Most *et al.*, chloroquine in therapeutic dosage produced no gastro-intestinal symptoms other than occasional mild nausea if the drug was taken by the patient in a fasting state. Dizziness and light-headedness that were probably due to chloroquine occurred rarely, and neither tinnitus nor visual disturbances were observed. In 20 per cent of a group of 284 patients in whom effort was made to elicit evidence of cutaneous symptoms through special questioning, pruritus was found to develop during the course of treatment; this pruritus was occasionally generalized but more often localized particularly on the palms and soles, and in a majority of cases it was transitory and slight in degree. Two and four-tenths per cent of the patients developed erythema, urticaria or a mild papular eruption. Chloroquine was found not to produce the disturbing symptoms of cinchonism incident to quinine administration, and it did not cause the kind of flare-up of eczematoid dermatitis or atypical lichen planus that sometimes follows the administration of quinacrine. Chloroquine does not discolor the skin. It should be stated, however, that the Board for Coordination of Malarial Studies recorded as occasional symptoms mild and transient headaches and visual disturbances that were readily reversible when [illegible] was stopped

[illegible] drug, which was developed by British [illegible] een principally reported upon by Maegraith and associates in England and by Fairley and his group in Australia. Maegraith's patients were returnees from the Indian, Burman and Mediterranean theaters of war, while Fairley used New Guinea strains in his trial; the important point is that vivax strains from all of these sources are

more prone to relapse than are our native strains in the United States, and hence the findings obtained in the tests in England and Australia may be taken to apply not only to our own returnees from the Mediterranean, Far Eastern and Southwest Pacific theaters but also to our own native cases.

Efficacy in Arresting Attacks and Preventing Relapses in Comparison with Chloroquine and Quinacrine.—It has not been shown that this drug is capable of effecting radical cure of vivax malaria; *i.e.*, the dosage which serves to arrest the attack does not suffice to prevent relapses. Indeed, both Fairley *et al.* (1946) and Maegraith *et al.* (1946) found that neither the fever, parasitemia nor other symptoms were subdued any more rapidly with paludrine than with quinacrine, and therefore by inference the drug does not compare very favorably from this standpoint with chloroquine. In fact, in a study on a smaller scale in the United States in which Jones *et al.* (1946) compared chloro- [illegible]

employment initiated by Fairley, found that if upon admission the patient is given a single dose of 300 mg. of the drug accompanied by a glass of water, he begins to feel better within a few hours and does not have a full rigor again, although there usually occurs a rise of temperature above normal on the "paroxysm day" immediately subsequent to treatment. The blood is usually [illegible]

Toxicity—Maegraith *et al.* reported no serious toxic side effects with the dosage scheme they employed, though with experimental doses of 500 mg. or more twice daily nausea and vomiting occurred occasionally. Fairley *et al.* also observed no significant toxic symptoms even when the 300 mg. dose was administered daily for twenty-one days; but when higher experimental dosage was used the subjects frequently vomited and occasionally red blood cells, sheets of epithelial cells and sometimes a hyaline or granular cast appeared in the urine. Gross hematuria developed in two instances on this high dosage. On [illegible]

dosage to be therapeutically effective.

[illegible]

as the dihydrochloride salt in tablets of two sizes, ¾ grain (50 mg.) and 1½ grains (0.1 gm.).

Dosage.—Customary adult dosage is 3 grains (0.2 gm.), with sodium bicarbonate 15 grains (1 gm.), taken with 200 to 300 cc. of water or an equivalent amount of sweet tea or fruit juice every six hours for five doses, this to be followed by 1½ grains (0.1 gm.) three times a day after meals for six days, so that the patient receives a total of 2.8 gm. in seven days. Children under six months of age are usually given two doses of 50 mg. at intervals of eight hours twice during the first day and then 25 mg. once daily for the next six days; children of six to twelve months receive double the above dosage. Einhorn and Tomlinson (1946) used the following dosage for older infants and children in Panama: 1 to 4 years inclusive, 50 mg. at intervals of six hours for three doses during the first day and then 50 mg. twice daily for the next six days; 5 to 8 years inclusive, 0.1 gm. at intervals of six hours for three doses during the first day and then 0.1 gm. twice daily for the next six days, 9 to 12 years, 0.2 gm. at intervals of six hours for three doses on the first day, and then 0.1 gm. three times daily for six successive days. It is easy, however, to agree with these observers in their contention that this is very arbitrary dosage and that one would do well to take into account the patient's size and weight and adjust the dosage accordingly rather than merely to dose according to the age attained. Infants and younger children take the drug fairly well if the tablets are crushed and mixed with the milk or with jam, syrup, etc.

Quinacrine is well absorbed by patients with diarrhea and dysentery, but it may have to be given intramuscularly if there is much nausea and vomiting; the intramuscular method of administration is described under the therapy of falciparum malaria.

Toxicity.—Quinacrine being a yellow dye causes the urine to assume the same color, and in perhaps 3 per cent of individuals who are being given the drug for the treatment of an acute attack it will cause yellow discoloration of the skin but rarely of the sclerae. This discoloration is not indicative of liver injury and usually disappears in a few weeks. Other annoying, but neither serious nor very frequently occurring, symptoms are headache, abdominal pain, nausea and diarrhea, any of which may persist for several days after the [illegible] suppressive dosage is

[illegible]

of the disease. However, the toxic psychosis which the drug is capable of causing during its employment for a brief period in the treatment of an acute [illegible] The psychosis begins either during the course of the

[illegible]

tion, disorientation, amnesia for recent events, and confabulation. The incidence of toxic psychosis in large series of treated cases was reported to be about 1 in 250 by both Gaskill and Fitz-Hugh (1945) and Sheppeck and Wexberg (1946), but an extremely variable incidence was reported by earlier authors. A few instances of convulsive seizures have also been reported. Recovery from these central nervous system intoxications seems practically always to occur rapidly after the use of the drug is discontinued, though Gaskill and Fitz-Hugh did report two cases in which typical schizophrenic reactions were *apparently precipitated by the malaria-atabrine episode* since the prepsychotic personality of the patients had given no hint of a latent psychosis.

Quinacrine may apparently be safely used in any stage of pregnancy, though it is the consensus that it should be withheld in pregnancy toxemia; *it*

does not cause the visual or aural disturbances characteristic of cinchonism and is usually preferred to quinine by the patient who has had experience with large doses of the latter.

Quinine with Pamaquine (Plasmochin) or Pentaquine, and Paludrine with Pamaquine.—A number of years ago Sinton, in India, showed that the simultaneous employment of quinine and pamaquine was very effective in reducing the relapse rate in vivax malaria, but the treatment did not become popular because of the fear of pamaquine toxicity. These toxic reactions involve many of the systems of the body gastro-intestinal tract symptoms, evidences of a toxic effect on the circulatory apparatus, changes in the blood varying from mild anemia to severe fatal hemolytic crises or agranulocytosis, methemoglobin cyanosis, muscular aches and pains and weakness, and signs of involvement of the central nervous system. Unfortunately many of the earlier and even some of the more recent reports of the high incidence and great severity of these reactions dealt with series of cases in which pamaquine was used with or shortly after a course of quinacrine and not with quinine as is here under discussion. A probable explanation for the greater toxicity of the quinacrine-pamaquine combination was offered in the observations of Kennedy *et al.* (1946), who found that quinacrine excludes pamaquine from the physiological mechanisms normally responsible for its metabolism and thus results in an abnormally high plasma pamaquine concentration. During War II the quinine-pamaquine matter was reinvestigated both by the British and ourselves. In England, Kelleher and Thompson (1945) treated 524 cases with the quinine-pamaquine combination and used 429 quinacrine treated cases as controls. Quinine, 10 grains (0.65 gm.) and pamaquine naphthoate, 1/6 grain (10 mg.) were given together three times daily for ten days. These were Mediterranean cases and five months after the treatment 34 per cent of the quinacrine cases had relapsed whereas only 10.3 per cent of the quinine-pamaquine cases had done so. In the United States, Most *et al.* (1946) treated seventy-two patients with Southwest Pacific vivax with quinine-pamaquine, using seventy-five quinine treated cases and sixty-nine quinacrine treated cases as controls. Quinine was given in a dosage of 15 grains (1 gm.) and pamaquine naphthoate 1/3 grain (20 mg.) simultaneously at eight-hour intervals for one day, followed by 10 grains (0.65 gm.) of quinine sulfate and 1/3 grain (20 mg.) of pamaquine-naphthoate simultaneously at eight-hour intervals for the next thirteen consecutive days. Quinine failed to prevent relapses during the observation period of four months in 89.4 per cent of the patients, quinacrine failed in 84 per cent, and quinine-pamaquine failed in only 11.1 per cent. These two studies provide undeniable evidence that the use of quinine and pamaquine in combination provides an excellent means of preventing relapses in vivax malaria through treatment applied during the acute attack without any follow-up drug administration as is necessary with both chloroquine and paludrine. Most *et al.* felt that, unless plasmochin alters the biology of vivax malaria so that very late relapses will occur in the majority of treated patients, one could look upon freedom from relapse during four months, which occurred in 90 per cent of their cases, as representing definitive cure for at least 80 per cent of the men so treated. No conspicuous or serious toxic manifestations from the pamaquine were observed in the series of Most *et al.*, though both this group and Kelleher and Thompson stressed the point that the patient should be under strict medical supervision in hospital

throughout this treatment. The latter observers said that if cyanosis or abdominal colic appears, pamaquine should be discontinued and the course completed with quinine only; of their 295 patients only three had to have treatment interrupted in this way, but in other groups in which perhaps unfamiliarity with this type of therapy made the medical officers more cautious it was considered advisable to stop the treatment in from 2 to 4 per cent of instances. And it seemed to be the consensus during the war that troops under combat conditions bore pamaquine very poorly. All observers are in agreement that dark-skinned races tolerate pamaquine less well than do the white-skinned. Einhorn and Tomlinson (1946) used the following pamaquine naphthoate dosage for children: less than 1 year of age, 1/12 grain (5 mg.) once daily; 1 to 4 years inclusive, 1/6 grain (10 mg.) once daily; 5 to 8 years inclusive, 1/6 grain (10 mg.) twice daily; 9 to 12 years inclusive, 1/6 grain (10 mg.) three times daily.

Pentaquine (SN-13,276) is a new antimalarial agent proposed as a substitute for pamaquine in combination with quinine in the treatment of vivax malaria on the basis of its lesser toxicity. Loeb (1946), in a statement for the Board for Coordination of Malarial Studies, said that the toxicity in therapeutic dosage is qualitatively the same and quantitatively approximately one-half to three-fourths that of pamaquine in adults. The toxic symptoms are occasional anorexia, abdominal discomfort or pain, and slight methemoglobinemia. In a series of 171 white volunteers taking the drug severe anemia occurred in only one instance. Leukopenia was not encountered but n [illegible]
mend [illegible]
ately [illegible]
grains (80 mg) of pentaquine diphosphate and 30 grains (2 gm.) of quinine sulfate, administered in divided doses every four hours for fourteen days This group had a relapse rate of 4 per cent while a similarly infected control group of eighteen, treated with purely suppressive drugs, had a relapse rate of 67 per cent. Seventeen patients with severe Southwest Pacific infections were also treated; this group had a relapse rate of 18 per cent as compared with a relapse rate of 98 per cent in the controls. This new drug will certainly bear watching.

The combination of 300 mg. of paludrine and 60 mg. of pamaquine naphthoate daily for ten days was tried by Fairley (1946) in Southwest Pacific cases. Two hundred and thirty-two patients so treated were compared with 223 patients receiving quinine and pamaquine under comparable conditions; the relapse rate was the same in the two groups but the average interval between treatment and relapse was 66 5 days in the paludrine-pamaquine series and 31.4 days in the quinine-pamaquine series. It was also said that the troops generally preferred paludrine-pamaquine to quinine-pamaquine because of their objection to the disagreeable symptoms caused by quinine. A follow-up report of this interesting study is promised.

Drugs of Minor Importance.—Since we now have three superbly fine synthetic antimalarial agents in chloroquine, paludrine and quinacrine, it becomes necessary to admit, though not without some sadness, that venerable old quinine has become a drug of relatively little importance when used alone in the treatment of vivax malaria. I shall therefore treat of it and totaquine rather briefly here.

Quinine Dosage and Toxicity.—The standardized adult dosage of quinine

sulfate in tablets or capsules is 15 grains (1 gm.) three times a day after meals for two days, following this by 10 grains (0.6 gm.) three times a day after meals for five days (total 16 gm. in seven days). I think it should be noted here, however, that Hiatt (1944) found the plasma concentration of any of the alkaloids of quinine markedly lower if the drug is taken immediately after a meal. Einhorn and Tomlinson (1946) used the following dosage, repeated three times daily at suitable intervals, in children. age less than 1 year, ½ grain (30 mg.); 1 year, 1 grain (60 mg.), 2 years, 2 grains (0.12 gm.); 3 and 4 years, 3 grains (0.2 gm.); 5 and 6 years, 4 grains (0.25 gm.); 7 and 8 years, 5 grains (0.3 gm.); 9 and 10 years, 6 grains (0.36 gm.), 11 and 12 years, 7 grains (0.45 gm.). If one wants to put quinine in solution the following is about the best that can be done in the way of disguising taste (and little enough it is!):

℞ Quinine bisulfate	ʒiiss	14.0
Aromatic syrup yerba santa (eriodictyon) to make	℥iv	120.0

Label As directed (A teaspoonful contains the equivalent of about 5 grains [0.3 gm.] of quinine sulfate.)

In American military circles the pleasant little custom prevails of bringing the sulfate into simple unflavored solution in water by the addition of concentrated hydrochloric or sulfuric acid at the rate of one drop of the acid to 5 grains of the salt in a drachm of water. This barbarism is best not attempted in civilian practice. The Coco-Quinine of Eli Lilly and Company, which is a chocolate, vanilla and yerba santa flavored suspension containing 10 grains (0.65 gm.) of quinine sulfate per ounce, is an excellent preparation to use in children if there is difficulty in getting them to take the drug disguised as in the above prescription, but of course it is somewhat expensive. Howie and Murray-Lyon (1943) found that despite precautions to insure that quinine was being regularly taken, 24 out of 100 malaria patients showed negative Tanret reactions in all or many of their urines during treatment and convalescence, their responses to quinine therapy comparing unfavorably with those whose Tanret reactions were regularly positive, so it would seem that quinine absorption from the gastro-intestinal tract under almost all circumstances does not perhaps occur with as great regularity as had been thought. However, it has been shown to occur very well in the presence of diarrhea.

It is not unusual for patients taking quinine to be made very uncomfortable by one or more of the following symptoms. nervousness, headache, giddiness, palpitation, tremors, nausea, disturbances of sight and hearing. Sodium bromide, 2 grains (0.12 gm.) for every 1 grain (60 mg.) of quinine, is often given to control these symptoms. Occasionally loss of sight and hearing has occurred and return of complete function has not always taken place upon cessation of the administration of the drug, however, such serious poisoning occurs very rarely. Idiosyncrasy is quite another matter, however, for patients truly hypersensitive to the drug may be upset by very small doses. Most usual signs of idiosyncrasy are skin rashes, gastro-intestinal disturbances, coryza, pseudo-asthmatic and anginal phenomena, purpuric and other hemorrhagic disturbances (including the blackwater fever type of syndrome) and agranulocytosis have been reported, and since this is an allergic type of reaction almost anything can be expected. The substitution of quinidine for quinine in cases of idiosyncrasy to the latter drug has been shown to be feasible. The alleged effect of quinine upon the menstrual flow has not ever been substantiated in a well studied series of cases, but it is certainly a relief to know that the newer

synthetic agents do not stimulate uterine contraction, since the impression that quinine in full dosage is contraindicated in the pregnant woman is certainly deeply ingrained in medical consciousness throughout the world despite the fact that there are some men of considerable experience who are certain that the drug is not contraindicated It seems certain, however, that quinine given to the pregnant woman is capable of causing serious visual and aural idsturbances in the infant, this has occurred extremely rarely to be sure, but it has occurred.

Totaquine.—During the early part of War II, when Java, the source of quinine, had been lost and the superiority of quinacrine (atabrine) to quinine had not yet been established, the U. S. Pharmacopoeia recognized the brown insoluble powder known as totaquine, which by definition contains not less than 7 and not more than 12 per cent of anhydrous quinine and a total of not less than 70 and not more than 80 per cent of anhydrous crystallizable cinchona alkaloids, these latter including cinchonidine, conchonine, quinidine and quinine. This definition permitted the use of Latin American cinchona barks which are relatively low in quinine content. Somewhat similar totaquine had been in use for many years in various parts of the world where the attempt had been made to supply a relatively cheap form of antimalarial drug for pauper native populations, and it has been the consensus that it is very effective in the treatment of the disease; indeed some observers have claimed for totaquine a greater value than for quinine. The most extensive study of American totaquine was that reported by Green (1945), in which it was found that totaquine used in the same dosage as quinine controlled fever in a period of time identical with that of quinine and caused the disappearance of organisms from the blood stream in practically the same length of time as the older drug; incidence of toxic symptoms was about the same for totaquine and quinine, but the nausea and vomiting caused by totaquine proved more disagreeable than any toxic symptoms of either quinine or of quinacrine which was used as control. The interval between attacks and subsequent relapses was somewhat shorter for cases treated with totaquine than for cases treated with quinine.

Other Drugs.—Penicillin and the antimony preparations have been shown to be utterly worthless in malaria. Sulfadiazine, and the anti-syphilitic organic arsenical and bismuth compounds, have been shown to have some limited ability to arrest the vivax attack, but since their therapeutic efficacy does not *compare at all favorably with the newer synthetic* antimalarial agents or even with the older quinine, and as they are all potentially much more toxic than [illegible] space with

[illegible] of the [illegible] vivax [illegible] ance in the [illegible] ence in the

econditioning program at Hammond General Hospital, [illegible] of primary mportance to assure the patient early that his chronic relapsing disease will eventually be cured without untoward and permanent sequelae. Experience in the war also taught us that the debilitation which we have been accustomed to associate with the idea of chronic malaria on the basis of experience of the disease among tropical natives and the malnourished poor white inhabitants in our own South is not an essential concomitant of the disease, for it was *noted*

among our healthy young soldiers who contracted malaria that if the symptoms of operational fatigue or other concurrent involvement, especially infections such as amebiasis and ancylostomiasis, were recognized and specifically treated, in most instances the patients recovered quite rapidly without any period of "postmalarial asthenia" despite the fact that they were continuing to have relapses at intervals. Tumulty *et al* (1946) concluded from a thorough *organic and psychological analysis of fifty malarious soldiers at the Eighteenth* General Hospital that the otherwise healthy young malarious individual is usually capable of remaining useful, even though sometimes in a limited capac-

to make a poor adjustment to malaria and to become incapacitated rapidly, and they found it frequently true that men transferred early to well-delineated duties commensurate with their capacities did extremely well and lost many of their chronic symptoms. This was also the experience of Gordon *et al.* (1945) at the Harmon General Hospital, and Coggeshall (1945) at the U. S. Marine Barracks at Klamath Falls, Ore. The idea, frequently expressed before and during the early phases of the war, that exercise provokes relapse was not borne out in the experience of any of these groups provided the exercise prescribed was commensurate with the individual's capacity to perform. However, patients suffering with malarial headaches are often intolerant to any form of physical exertion especially if performed in a hot sun. Since these headaches do not respond to the usual analgesic or sedative drugs, Zeligs (1945) reasoned that perhaps they might be explained on the basis of cerebral capillary stasis with resultant focal cerebral edema and anoxia, even though such a state of affairs has never been definitely shown to exist in vivax malaria. Zeligs used nicotinic acid to produce vasodilatation and to enhance cerebral blood flow in a group of twenty-five patients, of whom ten stated that the headache had disappeared entirely under the treatment, eight noted moderate relief and seven

days; in cases in which the headache recurred every day and was present on arising in the morning, 50 to 100 mg. nicotinic acid taken after breakfast usually gave relief for the entire day.

In cases in which there is an annoying amount of splenomegaly, Ascoli some

from an acute attack the subsequent relapses are remarkably mild and do not require the use of specific drugs. I have not seen a report of a thorough and unprejudiced study of this method in some country other than Italy, but Butler (1946) said that several very capable hospital groups in the United States had tried it without any success whatever. Podlesker (1944), in the Argentine, described the intravenous injection of 10 cc of a 10 per cent solution of calcium chloride on each of five successive days, the claims advanced for this type of treatment being similar to those put forward by advocates of Ascoli's method.

Most physicians in the tropics recognize the advisability of a change of
the sojourn in a tem-
"; residence in a rela-
ation though actually
this will take place just as well in any bracing northern climate. It has been generally held that sudden ascent into a high altitude, such as a journey by airplane above a 10,000 foot ceiling, is extremely likely to provoke relapse, but neither relapse nor parasitemia was observed within a period of seven days in Howe and Duff's (1946) group of fifty malarious individuals who were exposed for one hour to a simulated 18,000 foot altitude; there is reason to believe, however, that exposure in these cases to low pressure for a time sufficient to produce a well developed oxygen want might have altered the findings, at least that was the experience of Gajewski and Tatum (1944) in avian malarias. The fact that malaria is practically unknown in permanent settlements at very high altitudes is probably entirely due to the inability of the anopheline vector to survive there, for Garnham (1945) reported a localized outbreak of malaria at an altitude of 8,500 feet under conditions in which the mosquito was able to spend practically all of its life indoors.

The belief that surgical procedures are extremely likely to provoke malarial relapse was questioned by Kark (1946), in whose 176 patients operated upon without preliminary suppressive precautions the postoperative relapse rate was no higher than it would have been otherwise and bore no relationship to the major or minor variety of the surgical procedure; it did seem however that local anesthetics containing epinephrine were followed by a higher proportion of relapses than other forms of anesthesia. In a group of 147 patients who were given suppressive therapy before operation the incidence of postoperative relapses was practically the same as in the non-treated group, but in a third group of 1900 surgical battle casualties in whom suppressive therapy had been instituted a considerable time before the battle trauma and was continued throughout the period in hospital, postoperative malaria was virtually eliminated.

THERAPY OF MALARIAE (QUARTAN) MALARIA

In a comparison of the efficacy of chloroquine, quinacrine, quinine and
totaquine in seven
chloroquine gave t
order just stated.
evidence that quartan infections respond much more slowly to any of the drugs than do vivax infections. In thirty-five cases of persistently relapsing quartan in which quinine had been used according to various dosage schemes but without definite effect, Grabenko (1946) gave five or six intravenous infusions of 15 to 20 cc. of 1 per cent solution of methylene blue in 25 per cent glucose. He

felt that the results justified resort to this treatment when all of the specific antimalarials had failed to check the attacks—but methylene blue had its day a long while ago and I doubt if it will be revived.

THERAPY OF FALCIPARUM (MALIGNANT-TERTIAN) MALARIA

The Therapeutic Problem.—Falciparum malaria may be easily cured through the use of any one of the new synthetic compounds, *i.e.*, not only will the current attack be terminated but a short course of therapy will suffice to eradicate the infection completely so that it is unnecessary to continue with weekly reduced dosage over a long period of time as is the case in vivax malaria. Loeb (1946), in a statement for the Board for the Coordination of Malarial Studies, said that this may be accomplished with chloroquine by the three-day treatment method employed in vivax cases Fairley (1946) obtained radical cures with 100 mg. of paludrine three times daily for ten days, but Maegraith *et al.* (1946) preferred to use the 100 mg. dose only twice daily but

[illegible]

fulminating forms of malignant malaria it is mandatory that quinacrine or quinine be given parenterally at the earliest possible moment; indeed some men

[illegible]

from the gastro-intestinal tract; Beck and Cutts (1945) observed five such

[illegible]

disease.

[illegible]

tions and *especially avoiding speed.* If necessary in emergencies there should be no hesitation in cutting down upon the vein. This treatment may be repeated in from six to eight hours if the situation demands it. When the patient can take and retain oral medication he should be given a complete course of one of the newer antimalarial agents if available or otherwise quinine, dosage in either case being that previously stated for the oral administration of these drugs There are many men who throw up their hands in a gesture of horror at the mere thought of administering quinine intravenously, but as a matter of fact it seems that experience in War II proved that the measure is fully justified where the proper indications exist and that it is not excessively dangerous—testimony on both sides of this highly con-

troversial question is so voluminous that I cannot take up the space here to cite it. Most and Meleney (1944) stated that since rapid intravenous injection of quinine may produce a definite fall in blood pressure it is well to have at hand a sterile syringe containing 1:1000 epinephrine solution, of which 1 cc. may be slowly given intravenously in the event collapse occurs. Dreisbach and Hanzlik (1945) made an extensive experimental study of agents to combat the circulatory depressant action of quinine when given intravenously and found epinephrine the most effective; they also called attention to the fact that as long ago as 1931 Escher and Villequez, French Army surgeons, were employing epinephrine in combination with quinine intravenously. Hanzlik and Cutting (1945) recommended that 1 mg. of epinephrine (1 cc. of the familiar 1:1000 solution) be added to the quinine solution for intravenous administration and that the time alloted for injection of the quinine and epinephrine in saline be not less than thirty minutes. They felt the intravenous injection of quinine to be probably contraindicated in severe shock, especially hemorrhagic, pulmonary edema, cardiovascular disease, cyanosis, severe anemias and pregnancy. For my own part, I do not see why it would not be feasible to institute a slow intravenous quinine drip therapy in many cases of falciparum malaria after the 10 grain (0.6 gm.) dose has been given during the first half-hour. My point is that the total quinine dosage for the day should be administered by a continuous slow drip so that the organisms would be assailed steadily by a fixed level of the drug rather than by the high peak titers as occurs when administration is intermittent. Smith and I (1944) showed that something approximating this method was remarkably efficacious in experimental avian infections and I should like to see the idea put to clinical trial. During the late war the rumor went about that the circulatory depressant effects of large amounts of quinine given intravenously would be less if the drug is administered in blood plasma instead of in saline solution, but Marsh (1945) warned that troublesome clotting might ensue if this practice is pursued; I do not know whether this is true or not, but Quick (1946) showed that small daily doses of quinine sulfate by mouth cause no decrease in the prothrombin of the blood.

Quinine Intramuscularly.—It seems to me that the time has come for acknowledgment of the fact that the severe abscess at the site of injection of quinine in the gluteal region, even though it occurs very infrequently, is sufficient to contraindicate this method of administration in view of the fact that experience in War II showed the intravenous route to be quite safe under the conditions stated above. Nevertheless, a good many men are still clinging to the intramuscular route, and I therefore set down here what would seem to be the most acceptable formula; the hydrochloride is employed instead of the dihydrochloride since the acidity of the latter contributes toward the dangers of the procedure, and urethane or antipyrine is used to increase the solubility of the hydrochloride; the solution has been made a very dilute one in the further attempt to minimize quinine's tissue damaging action.

℞ Quinine hydrochloride . . . . gr. x 0.6
Urethane
or
Antipyrine . . . . gr. v 0.3
Water to make . . . . ℨiiss 10.0

Label. Sterilize by boiling and when cool inject 1 cc. for each 1 grain (60 mg.) of quinine desired.

In injecting quinine intramuscularly it is important that the needle without any solution in it be introduced first and then the syringe attached, and that at the conclusion the quinine syringe be replaced with one containing a little air or sterile water to be injected to clear the needle of solution before it is withdrawn. These injections must be made slowly and at their conclusion the area is to be gently massaged for ten minutes.

Quinine by Rectum.—For the adult, 30 grains (2 gm.) of the dihydrochloride may be dissolved in one quart (1000 cc.) of normal saline and given by slow rectal drip; 2 ounces (30 gm.) of dextrose added to this will enable one to supply specific drug, nourishment, fluid and salt. Of course the drug may also be given in a more concentrated solution through the rectal catheter as a retention enema, but in such a case it is probably advisable to cut the dose in half and repeat in a few hours. Quinine sulfate may be used in place of the dihydrochloride in preparation of the retention enema if it is mixed with a starch paste thin enough to run through the tube, or it may be dissolved with the aid of tartaric acid to avoid making the solution irritant. In children having convulsions, which is often the counterpart of the cerebral form of pernicious malaria in the adult, it is frequently necessary to employ quinine by rectum in somewhat larger dosage than would be indicated by the age and size of the patient; the buttocks should be taped together to insure retention.

Quinacrine (Mepacrine, Atabrine) Intramuscularly.—During the recent war, the studies of Shannon *et al.* (1944), which established the rationale of higher quinacrine dosage than had previously been employed, also pointed the way toward the substitution of intramuscularly administered quinacrine for intravenously administered quinine in such situations as we have under present consideration. Before the advent of the newer drugs many men had already switched to intramuscular quinacrine, finding it fully as satisfactory as intravenous quinine and freeing them from the necessity of worry over a possible severe circulatory reaction. Quinacrine dihydrochloride, 3 grains (0.2 gm.) in 5 cc. of sterile distilled water, is injected intramuscularly into each buttock with the usual precautions, giving a total dose of 6 grains (0.4 gm.). If necessary, one or two additional doses of 3 grains (0.2 gm.) may be given intramuscularly at intervals of six to eight hours. As soon as the patient can take and retain oral medication, quinacrine is given by mouth in such doses as to give a total by both routes of 20 grains (1.2 gm.) in forty-eight hours, followed by 1½ grains (0.1 gm.) three times daily after meals for five days (total 2.8 gm. in seven days).

Quinacrine Intravenously.—The studies of Shannon *et al.* (1944), above referred to, confirmed the earlier clinical impression that the intravenous administration of quinacrine is not advisable since acute toxic reactions may occasionally occur.

Chloroquine (Aralen) Intramuscularly.—The studies of Coatney, Cooper *et al.* (1947), at the National Institute of Health, with a chloroquine preparation specially prepared for intramuscular injection, will be watched with much interest.

Special Measures in Cerebral Cases.—These patients may quickly become dehydrated through reduction of fluid intake in their drowsy, comatose,

venous drip. In recent years it has been determined that the transfusion of plasma or whole blood, preferably the latter according to the findings of Feldman and Murphy (1945), often causes the disappearance of pulmonary edema and may indeed save the patient's life. Marriott (1945) pointed out the danger of asphyxia resulting from the tongue falling back, from gravitation of saliva into the trachea, or from the development of edema of the lungs He stressed the fact that such patients must never be left unattended and that the maintenance of the airway must be as much a matter of unremitting care with them as with patients under general anesthesia. Ransome *et al.* (1944) routinely nursed these patients in the Fowler position and found it to lighten coma, ease respiration, and lessen the frequency of pulmonary edema It is said that the inhalation of amyl nitrite may make the parasites more accessible to the specific drugs through dilatation of the vessels, but I much doubt the wisdom of this therapy; however, Most and Meleney (1944) stated that in their opinion it might be advisable to administer 100 mg. of nicotinic acid (not nicotinic acid amide) every hour intravenously to maintain the cerebral capillary vasodilatation—they cited a case, indeed, in which this procedure restored consciousness immediately They also said that sometimes spinal drainage may restore the patient to consciousness; Fitz-Hugh *et al.* (1944), concurring in this opinion, said that an initial tap is always justifiable and advisable in comatose patients or those with stiff neck, that the indications for repetition of spinal fluid drainage depend on the effect of the first one and the subsequent course of the illness (especially relapse into coma), and that neither clinically nor at autopsy had they observed any evidence of untoward results from spinal fluid drainage, which varied in amount from 5 to 25 cc. These latter observers also found that the intravenous administration of adrenaline (1 cc. of 1:1000 solution well diluted) was of value in certain comatose patients, though they did not think it should be used routinely and felt it probably contraindicated in shock and pulmonary edema, furthermore, they felt that its administration should be discontinued if the systolic pressure rises above 160 or the pulse rate becomes markedly accelerated or if other untoward symptoms appear. In a small group of cerebral cases whose mania was so wild that the individuals could not be easily handled in order to institute specific therapy, Gillett (1944) began his treatment by giving pentothal intravenously as for an ordinary surgical procedure, the patients being forcefully restrained for the few minutes required to make the injection. To his surprise the patients remained deeply asleep for many hours after the dose of pentothal and upon awakening seemed to have obtained exceptionally beneficial results from the specific antimalarial agents that had been administered in the interim.

SUPPRESSIVE TREATMENT (DRUG PROPHYLAXIS)

Comparison of the Drugs.—Experience with the new drugs chloroquine and paludrine has of course been slight in comparison with that gained through [illegible] of quinacrine [illegible] ne or [illegible] isons which may be quite simply stated.

Chloroquine (Aralen, SN-7618).—We have the statement of Loeb *et al.* (1946), summarizing a great deal of clinical investigation for the Board for Coordination of Malarial Studies, that effective suppression of both vivax

and falciparum malaria has been accomplished with chloroquine. We know that if quinacrine is administered in suppressive dosage for about a month after the last exposure to falciparum malaria the individual will not come down

regarding quinacrine either. Chloroquine's chief advantages over quinacrine as a suppressive agent, as matters stand at the present time, are the following: (a) it does not stain the skin, (b) it has a very trivial or almost nonexistent toxicity in suppressive dosage; (c) and the suppressive dosage of 0.5 gm. (2 tablets of aralen diphosphate) needs be taken only once weekly, though of course it must be taken on the same day of each week.

Paludrine.—Fairley's (1946) very thorough studies showed that 50 mg. of paludrine daily or 100 mg. twice a week constitutes effective prophylactic dosage against both forms of malaria; apparently the protection against falciparum is complete since when administration is stopped the patient does not come down with the disease, but even with dosage as high as 100 mg. daily continued for a month after the last exposure to heavy infection the patient is not fully protected against the development of vivax malaria after he ceases taking the drug. Satisfactory prophylactic dosage for children is considered

quine keen competition.

Quinacrine (Mepacrine, Atabrine).—It is now a matter of common knowledge that quinacrine proved to be an excellent suppressive agent during War II. If the drug continues to be taken for a month after leaving an area of exposure, falciparum malaria will not develop at all, though the individual is extremely likely to come down with vivax malaria in a month or more after ceasing to take the drug. The method of employing quinacrine which found highest favor was the taking of a tablet of 1½ grains (0.1 gm.) once daily, though numerous observers found it also satisfactory to administer the drug on the third and seventh day of each week in single dosage of 0.5 gm. Such studies as those of Brown and Rennie (1946) and Schaffer and Lewis

indicatec

therapy

faithfully

that the level of quinacrine concentration in the blood is not lowered by excessive perspiration. Since with suppressive dosage the maximum plasma concentration of the drug is not attained until after the fourth week, it seems highly advisable to institute the suppressive treatment at least a month in advance of exposure, or two weeks ahead with double daily dosage for that

region by boat causes postponement of the beginning of treatment since the taking of quinacrine may very considerably aggravate seasickness. The

there were no reactions. In this intradermally inoculated group, two children developed uncomplicated measles before the course of injections was completed and two had attenuated *measles fourteen days after* completion of the inoculations.

MELIOIDOSIS

Melioidosis is a glanders-like acute infectious septicemia of rodents, cats, dogs and possibly rarely horses in the Far East. Only about 100 cases have been reported in man in whom the disease usually takes the form of an acute or subacute sepsis, with pustules resembling those of smallpox appearing over the entire body in some cases; death occurs in a few days to weeks and at autopsy there are found visceral granulomata with multiple widely disseminated nodular abscess-like lesions. Infection is thought usually to result from the ingestion, in infected food or water, of the causative organism *Malleomyces pseudomallei* (*Bacillus whitmori*), but Blanc and Baltazard (*1942*) found fleas and mosquitoes capable of harboring the organism. Melioidosis is now included in the book because, during War II, Cox and Arbogast (1945) reported a case in our Armed Forces in Burma and Mirick *et al.* (1946) two cases on Guam.

THERAPY

[illegible] mentioned cases penicillin was used but was unable to [illegible]

MENINGITIS

(See *Meningococcal Meningitis* and *Sepsis and the Non-Meningococcal Meningitides*)

MENINGOCOCCAL MENINGITIS

(Cerebrospinal Fever, Epidemic Cerebrospinal Meningitis, Spotted Fever)

[illegible] from an active case or from a healthy carrier. In War II it was amply shown that the principal factor influencing the rate of dissemination of the disease at the Army posts was the presence of a high proportion of unseasoned troops, especially, according to Sartwell and Smith (1944), when there *was a rapid turnover of* such troops The predisposing influence of upper respiratory infection and of other debilitating circumstances has also been adequately demonstrated. Symptomatically, and indeed perhaps pathologically, the classical form of the disease can be divided into three stages, the first two of which are unfortunately not often recognized. The *first stage*

may simply be a carrier stage without symptoms, or there may be a tonsillitis, pharyngitis, or sinusitis, or a conjunctivitis with discharge containing

ence of

14) de-

camp

arrivals

or departures, the subclinical infection rate, a term they preferred to carrier

goes to bed, where he lies curled on his side, knees up and head bent toward them; he is extremely apathetic, loses both play of feature and modulation of voice, and when urged will complain in monosyllables of being "sore"

fluid and less frequently from the blood in this stage Accruing experience, however, has indicated that much would be gained by regarding meningococcic disease as a bloodstream infection of which the familiar cerebrospinal

be made to accomplish the diagnosis before actual signs of meningitis appear. (b) Acute fulminating septicemia with or without meningitis, manifested by sudden onset with marked prostration, rapidly developing profuse macular and petechial eruption, early and rapid circulatory collapse followed by death, often within a matter of hours This is the Waterhouse-Friderichsen syndrome; as originally described, hemorrhage into both adrenal glands was found upon postmortem examination but as the cases have increased in number it has become recognized that the same course may be run without adrenal hemorrhages having occurred before death For example, London and

his adrenal glands have been destroyed, the diagnosis is essentially a pathologic one and should be reserved exclusively for those patients in whom adrenal hemorrhage is demonstrated. Occasionally patients with this syndrome will collapse and be d[illegible] *premonitory* period o[illegible] rapidity with which th[illegible] see the spots appear as one looks at the patient. From the standpoint of a medical examiner, Martland (1944) made the point that death occurred so *rapidly in this* syndrome as sometimes to require differentiation in civilian life from food or chemical poisoning, trauma, negligence and even homicide. (c) A less severe form of bacteremia characterized by inflammation of one or more joints, a less intense eruption, often macular rather than petechial; and aching in the muscles of the extremities; parenthetically one should perhaps remark that Fox and Gilbert (1944) have not found that these cases with joint involvement are invariably otherwise mild At an Army post during the late war, Kinsman and D'Alonzo (1946) observed that for every two cases of meningitis there was approximately one case of meningococcemia without meningitis, and Sweet *et al.* (1947) recorded sixteen such cases in a total of 296 meningococcic infections treated in a civilian general hospital during a five year period. (d) A chronic form of bacteremia, in which bouts of fever, accompanied by joint pains and mild eruption, occur at intervals of weeks or months with intervening periods of relatively good health.

In a series of 207 patients with meningococcal meningitis of Sweet *et al.* (1945), treated in a municipal hospital, and ranging in age from a few months to seventy years, the most frequent complications were nerve palsies occurring in thirty-five patients. In their follow-up of these patients, admittedly incomplete, little or no recovery occurred in a large majority of those who became deaf whereas no patient with a motor nerve palsy was seen in whom the disability persisted for longer than six months after the onset of meningitis. Other complications in this series included ten instances of arthritis or tenosynovitis and four of purulent conjunctivitis, all of these complications being of short duration with no residual manifestations. In addition, one elderly patient developed extensive thrombophlebitis with secondary cerebral emboli and permanent mental deterioration. Before the advent of specific chemotherapy in this disease relapses occurred in about 50 per cent of cases; with the use of sulfonamides the incidence has been reduced to about 8 per cent.

The highest incidence of the meningococcal infections is in children under ten, then in adolescents and then in young adults. Late winter and spring usually marks the peak of the seasonal increase in cases Mortality varies greatly from year to year but prior to the use of sulfonamides in therapy it was always high—30 to 90 per cent or even higher.

So far as I am aware the first published accounts of meningococcal meningitis were those of Gaspard Vieusseaux (1805) at Geneva and L. Danielson and E. Mann (1806) in Massachusetts In 1811, the American, Elisha North, published a large monograph on the subject. Weichselbaum discovered the causative organism in 1887, and Flexner introduced the antiserum in 1909.

THERAPY

Sulfonamides.—The use of these drugs has completely altered the outlook in the meningococcal infections in recent years. When a sulfonamide is

promptly and properly employed there is usually a return of the temperature to normal and practically complete disappearance of the other acute symptoms within two to six days—first signs of improvement are often seen within a few hours of beginning the medication. Delirium subsides or the eye of the coma-

been 7.6 per cent if they had excluded such patients as actually died from some other conditions although the latter were initiated by the infection itself. These authors furthermore stated that had they merely reported the most recent winter's experience they would have had sixty-four cases and two deaths, a mortality rate of 3.2 per cent only, thus illustrating the variability of the disease. In the 207 patients treated in a municipal hospital by Sweet *et al.* (1945), the case fatality rate varied according to the age of the patient. There were no deaths in the thirty-one patients nine years of age or less, considered

between the ages of ten and forty years the case fatality rate varied from 5 4 to 9 3 per cent. In the fifty patients above forty years of age the death rate for the whole group was 24 per cent and varied from 18 to 32 per cent. These observers felt that the most important single factor in prognosis is the presence or absence

coma or delirium for twenty-four hours or more before treatment was begun, eleven died. Therefore it would seem that not only the presence but also the duration of coma is of great importance in determining prognosis in the individual case.

Sulfadiazine has proved more effective than the earlier sulfonamides in these infections, but the studies of Lepper *et al.* (1943) and Goldring *et al.* (1945) indicated that the newer drugs, sulfamerazine and sulfapyrazine, are

dose and the remainder divided and administered at intervals of four hours In slightly more than half of their cases the drug was given by vein during the first twelve to twenty-four hours, usually in a 5 per cent solution in distilled

water; in very severe cases the parenteral medication was continued for a longer period of time. It was the belief of these observers that the parenteral route should be employed only in severe cases and in those patients who are unable to take or retain oral medication, but the testimony of numerous physicians in War II supported the statement of Adams (1944) that the first dose should routinely be given intravenously for the reason that the patient's condition can change so rapidly that there is no justification, once the diagnosis has been made, for losing the time it takes for an oral dose to become absorbed. Adams (1944), Thomas (1943), and others have thought it sometimes advisable in fulminating cases to give an initial dose as high as 8 gm., but Appelbaum and Nelson (1944) believe this to be dangerous, especially if the drug is given by vein. To adults in coma, Goldbloom *et al* (1946) gave intravenously 5 gm. of sodium sulfadiazine in 1000 cc. of 5 per cent dextrose in saline, giving another 1000 cc. containing 2 5 gm. of the drug every six hours until the patient was able to take the drug by mouth, then 2 gm. of sulfadiazine were given by mouth every four hours for the remainder of the first twenty-four hour period following admission, thereafter 1 gm. every four hours until the temperature was normal, and then 1 gm. three times daily until all acute symptoms disappeared and for two additional days thereafter. There is no indication for the administration of the drug intrathecally since when given orally or intravenously it will reach a concentration in the cerebrospinal fluid of two-thirds to four-fifths that found in the blood.

Just what the sulfonamide blood level should be cannot be dogmatically stated, but it seems to be the consensus that 10 to 15 mg per cent should be striven for; indeed Thomas (1943) said that he did not consider it harmful to attempt to maintain a level of between 15 and 25 mg per cent provided the *likelihood of hematuria is reduced to a minimum* by *forcing fluids* and *giving* alkalis, while Goldring *et al.* (1945), with the same qualification, attempted to maintain a level of 20 to 40 mg. per cent However, Sweet *et al.* (1945) made a considerable contribution when they determined sulfonamide blood levels in 163 of their patients on the day they became afebrile. Twenty-seven patients had levels of less than 5 mg. per cent on that day, ninety-one patients (almost 50 per cent of the patients who survived) had levels of less than 10 mg. per cent, and only twenty-four had levels of 15 mg. per cent or above. The maximum blood levels on each patient were also obtained. For two patients who lived and one who died the maximum level was below 5 mg per cent; maximum levels below 10 mg. per cent were found in forty-five patients, from 11 to 20 mg. in 104 patients, and above 20 mg in only thirty-four patients who recovered. The relative frequencies of the various maximum blood levels in patients who died were approximately the same as those obtained in patients who recovered. This evidence seems to indicate that it is unnecessary to increase the dose of sulfonamides in order to obtain an arbitrary concentration [illegible] satisfactory

[illegible] patient receiving
[illegible] wenty-four hour

urinary output of at least 1500 cc., but the fever and sweating of these patients often quickly dehydrates them to such extent that an intake of 4000 cc or more may be necessary in order to maintain a 1500 cc. output; furthermore, since precipitation of the acetylated sulfonamide is much reduced in an alkaline urine, it is of advantage from the beginning to take steps to reduce urinary acidity. The frequent practice is of course to "push" fluids and give sodium

bicarbonate gram for gram with the sulfadiazine, but at one of the Army posts, Ochs and Peters (1943) routinized the matter very satisfactorily in the treatment of desperately ill patients as follows: preparatory hydration and alkalinization of the patients was carried out by the giving of 2000 cc. of 1/6 molar solution of sodium lactate intravenously before giving the sulfonamide. The first dose of sodium sulfadiazine was then given as a 5 per cent solution in 200 cc. of sterile distilled water After the sodium sulfadiazine was given, 1000 cc. of 5 per cent dextrose in saline solution and 1000 cc. of 5 per cent dextrose in sterile water were administered, the patient thus receiving a tota of 4000 cc. of fluid in twenty-four hours. The daily fluid balance and alkalini zation were carried out as indicated until nausea and vomiting ceased an the patient could take oral medication No further alkali was given after th first three days and no renal complications occurred

Regarding the value of spinal fluid examination as a guide to terminati of therapy, Appelbaum and Nelson (1944) stated their belief that und stress is often laid on the importance of the total cell count, for they often discontinued chemotherapy in the presence of a considerable pleocytosis; a rise in the sugar content of the fluid and a disappearance of the organisms were looked upon by them as the more important determinants, though control of the infection was not infrequently obtained before the return of the sugar to normal It would therefore seem that reliance on symptomatic improvement may be considered a safe guide to the termination of sulfonamide administration in the meningococcic infections

Toxicity—See the chapter on Sulfonamide Toxicity at the end of the book.

Penicillin.—The largest scale study of the use of this agent in meningococcal meningitis which has come to my attention is that of Rosenberg and Arling (1944), who treated seventy-six patients, seventy-five of the seventy-six patients recovered, the one fatality occurring in a patient admitted in a moribund state Ten thousand units of sodium penicillin, dissolved in 10 cc. of physiologic saline solution, were slowly introduced into the subarachnoid space after the usual type of diagnostic lumbar puncture and spinal canal drainage (the paramount importance of draining the spinal canal as completely as is feasible before injecting the penicillin was stressed). The intrathecal administration of the agent was repeated at twenty-four-hour intervals until clinical improvement, sustained fall in temperature, or a decrease in the meningeal signs was manifest and until the stained smears and cultures of the spinal fluid revealed no organisms. As penicillin was injected intrathecally with each lumbar puncture without awaiting the results of the bacteriologic studies, this plan in effect was tantamount to administering an additional dose of penicillin after the spinal fluid became sterile. Rosenberg and Arling felt that in some instances it was unsafe to withhold treatment pending the results of the spinal fluid cultures. The persistence of coma was regarded as an indication for further intrathecal therapy, and in the most severe infections and in those in which coma lasted forty-eight hours or longer, intrathecal penicillin was continued until the spinal fluid was bacteria-free on three successive days Penicillin was also administered either by the continuous intravenous drip method at the rate of 5000 units per hour or intramuscularly in doses of 15,000 units every three hours, the dose being reduced to 10,000 units every three hours if improvement was satisfactory. Generally, penicillin was given intravenously (40

units per cubic centimeter in a 5 per cent dextrose solution) for the first eight hours and continued intramuscularly thereafter. Patients with the fulminating types of infection received penicillin intravenously at the rate of 10,000 units per hour for four hours initially. Most of the patients recovered following only one or two intrathecal injections but some required as much as four to six. Intravenous and intramuscular penicillin did not prove effective in the treatment of such complications of meningococcemia as acute arthritis, epididymitis, orchitis, or pericarditis.

Meads *et al.* (1944) made the significant comment upon the above-discussed report of Rosenberg and Arling that they did not say how frequently sulfonamides were used in their cases and that no mention was made of any special effort to determine that point. Only in a single fatal case was it noted that the patient received both sodium sulfadiazine and penicillin. From observations in their own clinic and from many reports in the literature, [illegible]

[illegible] of the beneficial results; the patient is not always in condition to give a history of such therapy. In their own series of eight cases treated with penicillin alone a poor clinical and bacteriologic response was obtained as compared with sulfonamide-treated cases. They felt that the failure to obtain a proper distribution of penicillin throughout the cerebrospinal fluid after intraspinal injection probably explained the persistence of exudate and consequent pocketing off of organisms, adhesion formation and pressure difficulties, and emphasized the fact that the rapid and complete distribution of the sulfonamides throughout the cerebrospinal fluid results in the early resolution of exudate, demonstrable at autopsy. Appelbaum (1945) found the disease responding to penicillin in a less dramatic and slower manner than it does to the sulfonamides. In one of his cases the meningitis relapsed three times, necessitating the additional use of sulfadiazine to control the infection; he had never seen a relapse in any case treated with sulfonamides He thought penicillin to be of possible value as an adjuvant to sulfonamides in the treatment of the fulminating form of meningococcal infection and [illegible]

[illegible] there are many factors such as the virulence of the organism, the [illegible]ologic response of the patient, and the time interval between onset and initial treatment which must be considered in judging the value of the therapeutic agent, the fact that the combined treatment showed a mortality rate of [illegible] per cent in the cases receiving sul-

[illegible] a group of thirty patients having meningococcemia without meningitis into two groups, twelve of the patients being treated with sulfadiazine by mouth and eighteen with penicillin intramuscularly. There appeared to be little difference between sulfadiazine and penicillin from the standpoint of rapidity or degree of response to therapy, although the temperature response to penicillin was somewhat more rapid by about half a day. Smith and McHugh (1945) gave penicillin to a patient with meningococcal pericarditis as a complication in meningococcic menin-

gitis in which the organism was probably sulfonamide-resistant since it persisted in pericardial fluid despite the presence there of more than 8 mg per cent of sulfonamide, which was about the same level as there was in the blood, indeed the level rose to over 11 mg. per cent while the patient was growing increasingly ill. After withdrawing 430 cc. of pericardial fluid, 10,000 units of penicillin in 10 cc. of saline were instilled into the pericardial space, the dose being repeated in ten hours. The penicillin was injected in mid-afternoon and the patient showed improvement the next morning and continued to improve thereafter.

Serum.—It is now felt that chemotherapy has rendered treatment with serum as obsolete as routine spinal drainage. Mitman (1945), reviewing the records of two large-scale British studies, noted a fatality rate of 16 per cent where sulfonamides were used and over 50 per cent when serum alone was used. Furthermore, in every age group combined sero- and chemotherapy gave significantly worse results than the sulfonamides alone; of course the possibility that those who received combined treatment were more seriously ill than those who received the drug alone cannot be ruled out, but it would seem unlikely that this factor would account for the wide [illegible]

that recovery was related to the administration of the serum for a prompt improvement followed it, but in two other patients who recovered it was felt that the actual value of the serum in influencing the outcome was ques- [illegible]

Gregory *et al.* (1940) was 30 to 60 cc. for infants and young children, 90 to 120 cc. for older children and adults, the serum being diluted two or three times with physiologic saline solution containing 5 or 10 per cent dextrose; Hoyne (1940) used larger dosage, 150 to 300 cc [illegible]

made hourly in some cases, were necessary to relieve the embarrassed breathing and to prevent death from respiratory failure, eight of their patients had three or more punctures to relieve intracranial pressure. They emphasized, however, that the most frequent cause of restlessness in their semi-comatose and comatose patients was a distended bladder and that they never considered restlessness alone as due to increased intracranial pressure until catheterization had been done. In spite of the testimony in favor of spinal puncture, I think the reader will do well to heed Hoyne's advice of several years ago to avoid puncture if at all possible because frequent drainage is more likely to promote hydrocephalus than to prevent it, his opinion, based on a very large experience, was that "the fewer the punctures the fewer the hospital days."

Opiates.—Morphine or dilaudid is usually given without stint to control violent symptoms during the first twenty-four to forty-eight hours, though some observers believe they raise intracranial pressure and counsel against their use; Hoyne described the treatment of 134 patients, none of whom had been given any opiates.

Special Measures in Waterhouse-Friderichsen.—Kinsman *et al.* (1946) stated the principles of treatment in these cases to be: (a) to combat the infection with sulfadiazine or penicillin or both; (b) to combat shock with adrenal cortex extract, epinephrine, plasma and sodium chloride; (c) to combat anoxemia with oxygen; (d) to combat special complications as they arise (as, for example, hyperglycemia with insulin). But an analysis of the data in their own seven cases failed to disclose any one factor in therapy that was probably responsible for the two recoveries that occurred. For example, the largest dose of penicillin per hour was given in a fatal case, and while one recovered patient had received 116 cc. of adrenal cortex extract, the other had received only 2 cc., and a patient in one of the fatal cases was given 40 cc. Both the recovered patients were given 500 cc. of plasma while in the fatal cases one patient received none and the other only 250 cc., but no conclusion can be drawn from this since there was no evidence of hemoconcentration in the three patients on whom studies were made. Ceballos *et al.* (1945) suggested the following immediate intravenous dosage of adrenal cortical extract: patient of 5 kg., 5 cc.; 10 kg., 8 cc.; 20 kg., 12 cc.; 30 kg., 15 cc; adult, 25 to 40 cc. Then they would have the following doses given every three hours in conjunction with continuous drip fluid administration: patient of 5 kg., 0.5 cc.; 10 kg., 1 cc; 20 kg., 2 cc.; 30 kg., 3 cc.; adult, 5 to 10 cc. Their suggested dosage of desoxy- ... eight ... 0 kg., ... very ... lema.

continued to use antitoxin; they had no way of knowing whether it was helpful or not but they gave it to all of their six patients, two of whom recovered. Kinsman *et al.* (1946), pointing out that vitamin C is particularly abundant in the adrenal glands and that in acute infections its concentration in the body rapidly diminishes, and that in a few instances in patients with Addison's disease a definite parallelism between the degree of vitamin C deficiency and the severity of the disease has been shown, suggested the possibility that vitamin C may be involved in the collapse in Waterhouse-Friderichsen syndrome and that it might be worthwhile in the future to administer large doses of ascorbic acid to patients with this disease. They did not, however, offer any positive evidence of the value of this type of therapy.

SULFONAMIDE PROPHYLAXIS

War II presented the ideal conditions for a trial of sulfonamide prophylaxis in closed controlled populations. A number of such trials were made during ... will be summarized ... more than 15,000 soldiers at two Army camps when the disease was very prevalent during the spring of 1943, 18,800 soldiers in the same camps serving as untreated controls. The method employed varied only as to dosage of sulfadiazine in the two camps. In one camp the dosage was 1 gm. by mouth three times daily for three days, in the other camp the dose was 1 gm. twice daily by mouth for two days. In the first camp the carrier rate among the troops

to be treated was 36 per cent and in the control group 38 per cent. During the eight-week period of observation subsequent to the completion of prophylactic therapy no cases of meningococcic meningitis developed among the 8000 treated men while at the same time twenty-three cases occurred among the 9300 untreated controls During this period the carrier rate in the treated group went down to as low as 2 per cent and was never above 7.2 per cent

controls 9500, the carrier rate being 30 and 29 per cent respectively before the beginning of the experiment and the lows after the experiment being 0 and 29 per cent; seventeen cases of meningitis occurrred in the untreated group and two cases in the treated group, one of these two men, however, was probably infected elsewhere because he did not come down with meningitis until five weeks after he had been transferred to another organization.

From the study above summarized it may be concluded that a dose of 2 gm. of sulfadiazine daily for two days is highly effective in preventing the spread of meningococcic meningitis. Phair *et al* (1944), and Pilot (1945), indeed

be too strongly emphasized that Kuhns and his associates were convinced that the effectiveness of their prophylactic experiment depended upon. (a) treating all individuals in the group simultaneously, (b) treating all personnel who joined the group subsequent to the institution of prophylaxis before they were incorporated into the group, and (c) keeping the treated group closed to reinfection from outside sources The applicability of the measure under comparable conditions in civilian life was shown by Zeller (1945), who dosed 400 patients exposed to a case in a hospital for mental diseases without the development of a single secondary case And under special circumstances it may be useful even upon a much smaller scale For example, Rotondo and Handelman (1945), reporting the very rare occurrence of three cases of meningococcic meningitis simultaneously in the same family, suggested that in order to avoid such occurrences it might be wise to give all members of the family of any patient with meningococcic meningitis a day's supply of sulfadiazine as a prophylactic measure However, one should bear in mind the fact, stressed by Phair and Schoenbach (1945), that chemotherapeutic prophylaxis cannot control the incidence of reinfections indefinitely; *i.e.*, except during the relatively brief period of their activity the sulfonamides cannot confer free-

will depend entirely upon the prevalence of meningococcal infection among the people with whom he comes into contact and the effectiveness of that contact. The reader will be aware at once of course of the impossibility of protecting an entire open civilian population against infection through the employment of sulfonamide prophylaxis even were there not the factors of toxicity and sensitization to act as deterrents of the trial

MILIARY FEVER

(*English Sweat, Picardy Sweat*)

This is a disease of unknown etiology that occurs in limited epidemics of only a few weeks. There is high fever, great sweating, profound prostration and an erythematous rash with miliary vesicles. Between 1718 (when it was first described, though it had probably existed before) and 1861 there were about 175 epidemics recorded in France alone; Italy and southern Germany have also known the disease. The last reported outbreak occurred in France, in 1906. The mortality in the various outbreaks seems to have been quite variable, oftentimes being very low and at other times rising to 30 or 40 per cent. It is said that the last epidemic in France wiped out entire families in a few days, deaths however being almost entirely confined to fulminant cases and the fatal ending being rare after forty-eight hours.

In previous editions of this book I have said that it is very doubtful that this disease is the same as the "sweating sickness" that devastated England and the Continent several times in the fifteenth and sixteenth centuries, for John Kaye, or Caius, an eminent London physician who described the outbreaks of 1552, had nothing to say about an eruption of any sort. However, it seems that I should now stand corrected, for Tidy (1945) said that Caius' clinical descriptions were brief and applied only to the type of quickly fatal case in which no eruption develops; he felt that there is no substantial reason to doubt the identity of the English sweat and Picardy sweat.

THERAPY

I do not know of any treatment that warrants particular description

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MUMPS

(*Epidemic Parotitis*)

Mumps is an acute infectious disease probably confined to man, though allegations are sometimes made that it is seen also in goats, dogs and cats. It occurs all over the world and tends to become epidemic during the winter and spring months but is less contagious than measles, chickenpox and whooping cough. The greatest age frequency is between five and fifteen years, but the disease also often occurs among young men crowded together, as in barracks or ships or prisons, and among student nurses in hospitals. In the United States Army during War I, mumps stood third on the list of important diseases from the standpoint of noneffectiveness, ranking in this respect next to venereal disease and influenza, but Simmons (1943) stated that in War II the overall incidence of mumps was low, this latter fact probably being due, as pointed out by McGuinness and Gall (1944), to the fact that in the years between the two wars there occurred a great decrease in isolation in rural areas where many persons formerly reached adult life without exposure to the usual communicable diseases. However, Candel *et al* (1945), in a report somewhat later than that of Simmons, stated that in the Navy mumps still held third place among the diseases causing loss of time. Attacks in early infancy and in the years beyond forty are rare but not unknown. Unusual but well-authenticated second, third and

even fourth attacks are on record. A case has been recorded complicating pregnancy in which the symptoms were so severe as to jeopardize the patient's life.

The classic symptom of mumps is a swelling of one of the parotid glands, accompanied by stiffness of the jaws and pain which is accentuated upon opening the mouth or attempting to swallow There is usually a slight rise in temperature In most cases the opposite parotid swells also but involvement of the other salivary glands is relatively infrequent. Enlargement of the cervical lymph nodes is of common occurrence. A slow pulse rate and leukopenia with relative lymphocytosis are observable in practically all

et al. (1943) found blood diastase activity increased in mumps and Appelbaum (1944) observed an elevation of serum amylase in a great majority of cases Candel and Wheelock (1946), in attempting to confirm Appelbaum's observation, sought also to determine the effect of mumps on serum lipase since some observers have suggested that serum amylase elevation is due to a silent pancreatitis which might be expected to cause a concomitant elevation in serum lipase. They did indeed find serum amylase determinations

tients

that

creas.

The studies of Maris *et al.* (1946) indicated that in most normal individuals without a history of mumps the complement fixation reaction is negative; Enders *et al.* (1946), of the same group of investigators, showed that in adults their skin test is in most instances an even more sensitive indicator of past infection and hence of immunity than is the complement fixation

indicated that subclinical attacks by the virus of mumps occur so frequently as probably to account in young adults for about 33 per cent of past infections

Orchitis, which occurred most commonly about the sixth day of illness in Worden's (1944) series of 250 cases of epidemic mumps, is said ordinarily to have an incidence of only 18 per cent in boys past puberty and young men who are attacked by the disease, but in War II, Dermon and Le Hew (1944) reported an incidence of 35 per cent in 129 cases in a small task force, and a special commission of the United States Army Medical Department stated (Bulletin of the U. S. Army Medical Department, 79, 10, 1944) that in the moderate epidemics of mumps occurring in the South the incidence of orchitis approximated 30 per cent Orchitis is frequently preceded by

not seem that anyone has followed a series of cases to determine how many of these individuals become sterile but the occurrence is believed to be rare Loss of secondary sexual characteristics, libido, or the ability to perform the sexual act is extremely rare Gilbert (1944) concluded from an extensive survey that there is no direct relationship between mumps orchitis and later tumor development. The exact incidence of oophoritis is unknown

though it is doubtful if this complication is really less common than the
corresponding one in the male.
According to Lightwood (1946), mumps can lead to any of the following
neurological involvements: meningo-encephalitis, encephalomyelitis, labyrin-
neuritis, neuroretinitis, and retrobulbar neuritis; he reported an
local paralysis of the right leg. In 100
(1946), thirty-
ephalitis and
in ten other
nt of the
nervous
ed or the
central nervous system
found clini-
system involvement, the severity or number was not found. Candel *et al.* (1944) found clini-
and evi-
of epididymo-orchitis thirty-eight cases in his epidemic
nervous system in
ermanent residual
al loss appear and
total of 79 per cent
instances, corneal
Lippmann (1943). It is evident
ement in mumps is
are similar to those
meningitis have all
not a rare event and
fever. Orchitis,
interesting case there
observed in rheumatic fever. In Eagles' (1946)
occurred without primary parotitis. complicated by epididymo-orchitis without
was original meningo-encephalitis evidenced only by the rise and fall of
involvement of the parotids; mumps was during the course of the disease.
the specific complement-fixing antibodies there occurred femoral gland swel-
Schmidt (1945) reported two cases in which involvement and a third case, seen
ling and tenderness without salivary gland femoral gland involvement fol-
during the same epidemic, in which a similar Gellis and Peters (1944) re-
lowed "recovery" from parotid gland swelling over the sternum in 6
the occurrence of a soft pitting edema centering a diagnosis of mumps in
to the hospital with finding, possibly indicating a
from a camp in
the opinion that
edilection for the
so-called Stevens
mumps is basically
salivary glands, mature gonads, pancreas conjunctivitis, vesicular and sever
Johnson syndrome, *i.e.*, severe purulent and bullous cutaneou
membranous stomatitis associated with a vesicular according to Kove (1945
eruption, has been noted upon at least two occasions, though it is only spec
to have been immediately preceded by typical mumps these two entities.
lative that there may be any relationship between
Wollstein was, I believe, the first to show that the virus of mumps (first co
clusively demonstrated by Johnson and Goodpasture, in 1935) is present in t
mouth secretions of individuals having the disease. Droplet infection mig
therefore be expected to be the rule, since transmission can take place bef
the swelling appears; Habel (1945) said it has been noted that when mum
occurs concomitantly with upper respiratory infections it tends to spread m
rapidly than ordinarily because of the sneezing and coughing. We do not as
know whether there are many, or any, individuals who are carriers of
mumps virus. A quarantine period of two or even three weeks is often enfor
but since experience indicates that communicability very rarely extends

it is useless to operate when the process is already on the wane; they stated also that operation is not indicated in mild cases or those in which an epididymitis predominates. Both McGuinness and Gall (1944) and Finn and Palmberg (1944) found this operation of some benefit in a small series of cases Nixon and Lewis (1946) felt that the incision of the tunica albuginea, as advocated by Wesselhoeft, was too radical a procedure to be done routinely and that the simple drainage of the hydrocele fluid might give equally satisfactory results. This viewpoint seems to have been borne out in their experience in operating sixty-six patients in whom a small incision over the anterior surface of the scrotum on the involved side was carried through the skin and subcutaneous tissues until the tunica vaginalis was exposed; this was then grasped by clamps and incised, the hydrocele fluid draining out under considerable pressure usually, a small drain was inserted beneath the tunica vaginalis and the wound closed. After operation most patients reported immediate alleviation of extreme pain and others showed improvement within a few hours with relief not only from pain but headache, nausea, etc. Within twenty-four hours the local swelling was considerably reduced and the testis could be palpated with little discomfort to the patient; drainage was maintained for at least twenty-four hours. In most cases a significant drop in temperature occurred within twelve hours and it had returned to normal in an average of 2.1 days Follow-up examinations on twenty-seven of the sixty-eight patients, made at irregular intervals from three months to two years following the operation, revealed no evidence of testicular atrophy other than a slight degree of softening of the testis in twenty-six; the remaining patient showed definite atrophy of the involved testis six months following surgery.

PROPHYLAXIS

Leaders in this field are extremely skeptical of the prophylactic value of any materials of human origin containing mumps antibody. Enders (1946) said that a practical method of serum prophylaxis is not available and that, furthermore, unless some means of greatly increasing the neutralizing factor is discovered there would seem to be little likelihood that passive immunization in mumps will prove to be successful in the future. He pointed out that the gamma globulin concentrate used by Gellis *et al.* (discussed above) represented an amount equivalent to 400 cc. of convalescent serum or 200 cc. of normal gamma globulin and that even if such amounts were readily available in the form of serum it would be impracticable to administer them. Efforts are nowadays being made to develop vaccination as a protective measure. An agent is not as yet available for employment in general practice, but the very thorough study of Stokes *et al.* (1946) indicated that vaccination with their formol inactivated virus apparently induced increased resistance in about half of the children whose immunologic status was subsequently tested by experimental inoculation of pathogenic material. Perhaps, however, it would be well to bear in mind in connection with this whole matter of prophyl- ... before the age of puberty is very rarely ... ictic agent is going to ... than good.

MYCOSES

ACTINOMYCOSIS

Actinomycosis is a chronic infectious disease caused in about 90 per cent of instances by the ray fungus *Actinomyces bovis*, which probably exists normally among the abundant flora of the alimentary tract and gains access to the tissues through microscopic lesions, carious teeth, wounds made by penetrating foreign bodies, or reaches the respiratory tract by aspiration from the mouth and pharynx. The disease occurs quite commonly in cattle ("lumpy jaw"), sometimes in horses, hogs and sheep, and more rarely in other animals, but the fact is not yet firmly established that it can be conveyed from cattle to man, or indeed from man to man. Though looked upon as a rare disease, recent statistical studies tend to show that it occurs with much greater frequency than has heretofore been believed. Most of the cases in the United States have been seen in the upper Mississippi Valley and the northwestern states; country folk are much more often affected than city dwellers

The essential lesions of the disease are multiple, more or less painless, abscesses, usually surrounded by a considerable area of proliferative tissue. Discharging sinuses develop from the abscesses, and the process extends by continuity of tissue or sometimes by metastasis. Sixty per cent of reported cases have been in the region of the head and neck, usually beginning about the jaw, and here the diagnosis is not difficult In about 20 per cent of cases some abdominal organ is primarily affected; here the diagnosis is more difficult until the lumpy process extends to the abdominal wall and a characteristic sinus appears. In approximately 15 per cent of cases the involvement is thoracic with physical signs usually indistinguishable from pulmonary tuberculosis until perforation of the external wall takes place. Rarer forms of the disease may occur anywhere in the body, these cases being often caused by the aerobic organism *Nocardia asteroides*

Under proper treatment the prognosis may be considered fair in the head and neck cases, very bad in pulmonary and perhaps slightly better in abdominal cases

THERAPY

Sulfonamides.—There have been a number of reports, usually of only a single or a few cases, of the successful use of these drugs Hollenbeck and Turnoff's (1943) jaw case was apparently quickly terminated, Ladd and Bill (1943) and Pillsbury and Wassersug (1944) each reported an apparent cure in a pulmonary case and Watkins (1944) two such cures. The experience of Dobson and Cutting (1945) in the treatment of sixteen cases in which penicillin was used alone in three, sulfonamides alone in ten and the two agents together in three indicated that both penicillin and the sulfonamides are highly effective drugs in the treatment of actinomycosis but that perhaps sulfadiazine in adequate dosage is more effective than penicillin; this seemed also to be the conclusion of Lamb *et al.* (1947). Dobson and Cutting felt, however, that different strains of actinomyces vary considerably in their susceptibility to these drugs. In the two pulmonary cases of Kay and Meade (1945) partial symptomatic improvement resulted from the combination of penicillin and the sulfonamides, but apparent cure was not achieved until pulmonary resection in combination with this chemo-

therapy was performed. Morton (1940) failed with the sulfonamides in his two cases, Harris and Priestley (1944) failed in their case, and Clemens (see below) succeeded in his case with thymol after a sulfonamide had failed.

Penicillin.—The record of this agent is good but not brilliant. Dobson and Cutting (1945) obtained rapid and apparently complete healing in an extensive cervicofacial case that had resisted iodides and roentgen therapy during the preceding three months. For the first six days penicillin was given by continuous intravenous drip for a total dosage of 1,030,000 units; then during the next thirty-two days the patient was given 120,000 units daily broken up into three hourly intramuscular injections, so that the total by all routes was 4,655,000 units. Improvement was steady and eight months after leaving the hospital the patient was still entirely well with no induration or swelling of the originally involved area. In another cervicofacial case apparent cure was achieved in seventeen days with a total dosage of 1,560,000 units. In a third case, one of pulmonary and retroperitoneal actinomycosis, the patient was given penicillin intramuscularly throughout, receiving 200,000 units daily for the first seventeen days and 120,000 units daily for an additional twenty-one days Prompt and decided improvement occurred but it was not considered that the patient was cured and he was to be closely followed. McCrea *et al.* (1945) obtained very rapid and apparently complete cure in a case involving the soft tissues of the neck by the initial administration of 120,000 units of penicillin followed by 80,000 units intramuscularly every four hours until the patient had received 7,000,000 units. There was marked decrease in the swelling and discharge from the draining sinuses during the first seventy-two hours, at ninety-six hours purulent discharge had completely ceased and only a thin serous discharge was occurring; no discharge was evident on the ninth day, on the seventeenth day the sinuses and the draining incision had completely healed and only a small amount of induration remained around the sites of the former sinuses and incision; by the twenty-seventh day the induration had completely disappeared and there were no enlarged lymph glands in either the anterior or posterior cervical triangles—this was still the state of the patient when examined again after the lapse of four more months Walker and Hamilton (1945) successfully treated six cases with approximately the same dosage as McCrea *et al.* b extending the therapy over a considerably longer period of time; McCre *et al.* in commenting on these cases repeated the statement of their belie that the key to cure of the disease with penicillin lies in the administratio of large doses rather than in prolonged treatment. And there are several other reports of the successful use of penicillin. Perhaps one should note that in a case of Hendrickson and Lehman (1945) 10,000 units in 2 cc. of saline was twice injected directly into the mass after a small quantity of pus had been aspirated early in a course of treatment that lasted sixteen days with a total of 2,000,000 units of penicillin being administered parenterally; the patient was asymptomatic upon reexamination six months after leaving the hospital. But in Hudson's (1943) case an actinomycotic infection of the neck relapsed with the primary organism still present while under penicillin treatment although the secondary staphylococcus infection was eliminated. Three of the seven cases of Lamb *et al.* (1947) responded well, but the other four did not do as well as on sulfadiazine. And Herrell *et al.* (1944) reported the use of penicillin in twelve cases of actinomycosis with a satisfactory result in only two, a doubtful result in eight, and frank failure in two.

Iodides.—Sodium or potassium iodide used to be considered specific in a limited way in actinomycosis, but nowadays much doubt is felt of their real effectiveness Certainly their use in large doses must be persisted in for a long period of time—so long indeed in many instances that one must wonder whether it was really the iodides that finally produced whatever amelioration was obtained. Fortunately, most patients tolerate the drug well. I recall a case in which I gave 640 grains (42.6 gm.) of sodium iodide daily for a period of many months, 60 grains (4 gm.) intravenously and the remainder by mouth. During this time the patient was delivered of a normal baby and neither the mother nor the child showed any signs of iodism. Dosage even much higher than this has been employed not infrequently.

Thymol.—Myers (1937) reported good results with thymol administered in capsules of 22 to 30 grains (1.5 to 2 gm.) daily or on alternate days; in some instances [illegible]

[illegible] good success with thymol, combining its use, however, in most instances with the emplc [illegible]
curred un [illegible]
proved in [illegible]
breakfast [illegible]
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reported the progressive improvement and apparently complete recovery of a patient with primary pulmonary actinomycosis under thymol.

Surgery.—It is now the consensus that surgery should be boldly and persistently employed wherever the involved tissues can be radically curetted or widely excised. Wangensteen (1938), at the University of Minnesota, said that having set out to make a comparative study of iodides, surgery and irradiation, he obtained such satisfactory results with surgery that he never got around to trying the other measures. Furthermore, he learned that mere curettement and keeping the wound open by packing is just as effectual as excision. Cutler and Gross (1940) felt that the advances made in thoracic surgery in recent years justify very bold attempts to save life in apparently doomed pulmonary cases. Fuller and Wood (1945) reported what they believed to be the only recorded cure (based on fifteen months postoperative observation) by partial gastrectomy of primary gastric actinomycosis.

X-Ray.—Roentgenologists think very well of their results not only in the apparent but also in the deep-seated lesions. Auster (1940), in a review of the entire subject of actinomycosis, expressed the opinion that x-ray will undoubtedly play a more important part in the handling of this entity as time goes on Cutler and Gross felt that the relative innocuousness of the procedure often makes trial of x-ray worthwhile. In the case of Rashbaum and McIntosh (1944) in spite of hysterectomy and bilateral salpingo-oophorectomy followed by large doses of potassium iodide, there was prompt recurrence in the abdomen; roentgen ray treatment resulted in disappearance of the recurrences

Blastomycosis

North American blastomycosis (Gilchrist's disease) is an infectious but apparently noncontagious disease caused by *Blastomyces dermatitidis*, the portal of entry of which is the respiratory tract or skin. The impression that most cases in the United States have been reported from the vicinity of Chicago and from the state of Louisiana seems to be false, for though many cases have been seen in both Illinois and Louisiana, there is a wide scattering of reports throughout the country and some from Canada. The disease usually affects the skin only, but systemic involvement occurs not infrequently; in the latter instances the lungs are involved in about 95 per cent of the cases, the long bones sometimes, the intestines never.

Jacobson and Dockerty (1943) reported four cases in which the epididymis was involved, the condition clinically simulating tuberculous involvement of that structure. The cutaneous lesions take the form of papules, pustules, nodes, abscesses, or ulcers, and this form of the disease runs a course of many years during which active and quiescent periods alternate; when there is involvement of internal organs the prognosis is very bad. In the pulmonary cases the presenting symptoms are usually not easily distinguishable from those of tuberculosis.

South American blastomycosis (Lutz-Splendore's disease) is a chronic granulomatous disease of the mucous membranes of the mouth and the regional lymph nodes, the skin of the face and the internal organs; it has been divided into three distinct types, the mucocutaneous, the lymphangitic and the visceral. In this disease the portal of entry is the mouth, the intestines are often infected, and in only 15 to 20 per cent of the cases are the lungs involved. South American blastomycosis is said to be caused by three distinct species of *Paracoccidioides*, but Conant and Howell (1942) placed them all in the genus *Blastomyces* as a single species, *B. brasiliensis*.

THERAPY

Downing and Conant (1945) stated that treatment should not be begun in any case of North American blastomycosis until an intracutaneous skin test with 0.1 cc. of heat-killed vaccine of the fungus has been done to determine the sensitivity of the patient to the fungus or its products, Martin and Smith (1939) having shown that lesions of patients sensitive to such materials rapidly spread when iodides or x-rays or both are used. Patients found sensitive should be desensitized with gradually increasing doses of vaccine before beginning other treatment. Bush (1941) felt that the improvement in his case was due to supplementing large oral dosage of iodides by the daily intravenous administration of 15 minims (1 cc.), later increased to 30 minims (2 cc.), of compound solution of iodide (Lugol's solution) plus 15 grains (1 gm.) of sodium thiosulfate, x-ray therapy was simultaneously employed in this case. [illegible] there is involve-

[illegible]

apparentl [illegible]
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that the [illegible]
dermatitidis, feels that the use of these agents in North American blastomycosis is not indicated. In those rare cases where it is possible, total excision of the affected part is possibly the ideal treatment, but according to some observers

it must be excision and not merely curettement, for this latter procedure is thought to have been responsible at times for a spread of the disease. Copper sulfate has been used effectively in some cases in doses of ¼ to 1 grain (15 to 60 mg.) three times daily by mouth. X-ray therapy seems to have proved itself definitely useful; irradiation in conjunction with iodides was apparently successful in two of the four cases of blastomycotic epididymitis of Jacobson and Dockerty (1943), but Hemphill and Noojin (1942), while feeling that this type of therapy is likely to be effective in skin cases, thought that it might be expected to be unavailing in deep lesions with bone involvement. In the disseminated form involving the internal organs all therapy seems to be hopeless, the success with iodides in a single pulmonary case of both Decker (1939) and Wylie and De Blase (1944) probably being the exceptions to prove the rule. Fishman (1944) successfully treated a case with ether, in the case of Friedman and Signorelli (1946) ether therapy failed, but admittedly the case had a very poor prognosis from the start. In Fishman's case ether was applied locally to the skin lesions and was used to irrigate the osteomyelitic infection of the bone; in addition, 4 ounces of ether in an equal amount of oil were given rectally after a soapsuds enema on nine consecutive days. Thereafter the rectal ether-oil was given every other day for one week and then once weekly until the patient was discharged from the hospital, improvement having been constant and there being no evidences of any infection at the time of discharge, upon autopsy following death from another cause several years later there were found no evidences of blastomycosis nor any pathologic effects from treatment.

It has been stated that the South American cases are invariably fatal if untreated and that the iodides usually cause the lesions to spread; in this connection Downing and Conant suggested that the use of desensitizing vaccine before iodide treatment is indicated in the South American cases as well as in the North American cases. According to these latter authors recent reports have shown that the sulfonamides give almost immediate relief with the slow healing of lesions in the South American cases, but that they must be used in daily dosage over long periods of time, in some cases as long as one to two years.

CHROMOBLASTOMYCOSIS

This is a fungous disease of world-wide distribution but of rare occurrence. Binford *et al.* (1944) reported what was apparently the tenth case in the continental United States, but Emmons *et al* (1941), in reporting the sixth case, considered it likely that numerous other cases have hitherto gone unrecognized. Calero (1946), reporting two cases from the Isthmus of Panama where another case had previously been reported, brought the total diagnosed in the whole world to 154 cases. This mycotic infection, with *Hormodendrum pedrosoi* or several related organisms such as *Phialophora verrucosa* in the causative role, has been much studied by Carrion and his associates in Puerto Rico and Moore and his group in Argentina. Pardo-Castello *et al* (1942), confirming Weidman's earlier statement that this disease was being encountered in Havana also, reported thirty-one cases observed in Cuba. Classically the disease, which is often associated by the patient with injury by wood or vegetation, presents as a slowly progressing group of pink or violaceous, verrucous or papillomatous lesions, usually on the legs or feet; there are often cauliflower-like excrescences which readily ulcerate. But many of the cases have differed widely from this description so that ap-

parently clinical recognition of the entity without laboratory aid is not easy; some dermatologists feel that perhaps some cases now being diagnosed blastomycosis are in reality chromoblastomycosis.

THERAPY

It has been the impression that these cases often respond well to iodides but these classical agents were found worthless by Pardo-Castello; he preferred intensive roentgen therapy for the superficial types and electrocoagulation for the more extensive and infiltrated conditions. In one of Calero's cases after the excision of the warty masses by electrocautery the whole surface was electrocoagulated especially on the border. The healing was slow, and when complete repeated scraping did not show sclerotic cells; nevertheless for prophylactic purposes the patient received a series of ten irradiations. In the case of Snow *et al.* (1945), the lesions had remained healed seven months after removal by curettement and cauterization. Keeney (1945) felt that the use of sulfamerazine is warranted since he and his group had demonstrated *in vitro* the complete inhibition of *Phialophora verrucosa* by this agent; penicillin was not found to inhibit growth of the organism. Conant *et al.* (1944) stated the opinion that amputation should not be done since the lesions rarely become infected secondarily and the disease does not become generalized.

COCCIDIOIDOMYCOSIS

This disease is caused (in North America at least) by the fungus, *Coccidi-* ... first recognized endemic area was ... Valley in California, but it is now known that cases can be contracted along the western slopes of the Coast Range in the coastal countries and in Southern California inland from the Pacific. It seems also that Southern Arizona is badly infected and that Southern Utah, West Texas and probably New Mexico are also endemic areas. A large ... dry Chaco ... e radically ... nan (1936) proposed for this latter disease the designation "paracoccidioidal granuloma (Almeida's disease)." Dickson's studies, begun in 1937, introduced the viewpoint, for which ample confirmation has now been found, that "valley fever" of the San Joaquin Valley is the primary acute manifestation of the ... malady the patient comes down with acute ... chills and night sweats, great prostration, sometimes anorexia of such degree that much weight may be lost in a short period of time, backache and sometimes signs indicating meningeal involvement. In some instances a fine generalized rash occurs during the early days ...

pulmonary cavitation may ... and is rarely discovered. A ... Gilmore (1946) stated the opinion that a pulmonary lesion diagnosed by roentgenogram in an individual with a positive coccidioidin and tuberculin skin test may be considered most likely to indicate coccidioidomycosis if the lesion is nodular, round, discrete, less than 3.5 centimeters in diameter.

of a density less than calcium but greater than the usual vascular density in the hilum of the lung, and if it is associated with suggestive or definite hilar adenopathy. In 1940, Smith reported 432 diagnosed cases of this "valley fever" that had occurred in a period of seventeen months; the largest single epidemic that I have seen described was that of Willett and Weiss (1945) which involved eighty-three cases from an Army camp in Southern California during War II. Sometimes recovery from the acute attack occurs quite promptly but in many instances the illness lasts for a number of weeks before terminating in the form of an arrested infection of an essentially benign nature. Smith *et al.* (1946) said that sensitivity to the inhaled fungus as manifested by a reaction to coccidioidin develops ten days to a month and a half after infection is acquired, the incubation period from inhalation of the fungus to the development of the acute symptoms seeming to lie between seven and possibly thirty days.

In addition to frank cases of the nature described above there occur many inapparent affections; four-fifths of the long-time residents of the San Joaquin Valley have been found to have positive skin tests, and infection of cattle, sheep, dogs and small rodents has been shown to be very common in the endemic areas. Sweigert *et al.* (1946) said that of 200 enlisted men without a history of clinical infection but with up to eighteen months residence in the endemic area, 12 5 per cent reacted positively to the cutaneous coccidioidin test. Willett and Weiss (1945) found the coccidioidin skin test the most helpful single diagnostic reaction when used in conjunction with other aids, *i e*, travel history, roentgenogram, sedimentation rate (increased on admission in all their patients), differential blood count (eosinophilia in all their cases), and serological studies (most of their patients showed moderately high initial titer of precipitins followed by variable though consequential titer by complement fixation). They placed sputum examination last in their list of diagnostic aids. It seems that the recovered individual retains a high degree of immunity and will still react vigorously to coccidioidin for nearly thirty years after he has left an endemic area

It is estimated that usually in not more than one infection in 500 or 1000 does the fungus disseminate, but when this dissemination does take place it usually occurs in a few weeks or months after the infection has been acquired except in the rare instances in which it occurs in the initial illness without any interlude. Willett and Weiss (1945) recorded the unusual occurrence of dissemination in 4 per cent of a relatively small series of cases; they also found a higher rate of dissemination in colored than in white patients, confirming a long-held impression that dark-skinned races handle this disease poorly. Sweigert *et al* said that dissemination after several years as the result of endogenous reactivation, while admittedly a possibility, must be extremely rare if it occurs at all Dissemination means the development of the classical coccidioidal granuloma, which is looked upon as a disastrous occurrence The symptomatology of the progressive form of [illegible]

tuberculous meningitis without other evidences of dissemination However, in the main the mimicry of tuberculosis seems to be very close since there occur involvements of bones and joints, trachea, peritoneal cavity, lymph

nodes and even the occurrence of verrucous skin lesions, but it seems that coccidioidal enteritis does not occur nor has anything exactly comparable to tuberculous nephritis been reported. Demonstration of the fungus in the sputum is said practically always to be possible in this progressive form of the disease. Regarding the possibility of the transmission of coccidioidomycosis from man to man, which is commonly believed not to take place, it should be noted that Rosenthal and Routien (1946) transmitted the infection by bronchial instillation of spherules from man to animal and from animal to animal; these findings should perhaps alter our stand regarding the isolation of diseased patients.

THERAPY

In the acute form of the disease no form of specific chemotherapy has proved effective. Smith (1943) said that none of the sulfonamides was useful nor was thymol or iodide; Goldstein and McDonald (1944) also found sulfonamides of

penicillin in their single case; Kay and Meade (1945) failed with penicillin in two cases. Symptomatic treatment, and especially rest, are indicated. Smith (1943) said that except for isolation, the patient should be treated as though he had tuberculosis until he has recovered clinically, his sedimentation rate is well back to normal, his roentgenogram indicates that any lesions are regressing steadily and the titer of the serologic test is low or falling. His opinion was that if a pulmonary cavity has not closed after a few weeks of rest pneumothorax

colloidal copper, the 5-cc. ampule intramuscularly at four-day intervals; (d) vaccine and foreign protein shock therapy; (e) thymol by mouth, beginning with 15 grains (1 gm.) daily and working up to four times that amount until a total of 104 gm. has been given in twenty-four days, administered (50 per cent) in olive oil in capsules during meals, 33 per cent used for irrigation also (Sox and Dickson, 1936); (f) tartar emetic and x-rays: the antimony potassium tartrate from 2 to 8 cc. of a 1 per cent solution intravenously on alternate days, ½ skin unit of unfiltered roentgen rays at ten- to fourteen-day intervals (Tomlinson and Bancroft, 1934). It was not apparent that the sulfonamides, penicillin or atabrine was of much value in the cases of Denenholz and Cheney (1944). Arnold and Levy (1946) reported a case of coccidioidal meningitis that did not respond to penicillin given intrathecally; the patient died. In an occasional case early and radical amputation has cured a single lesion, but unfortunately other lesions occur elsewhere due to the disseminating nature of the process.

CRYPTOCOCCOSIS

(Torulosis, European Blastomycosis, Busse-Buschke's Disease)

This is a disease of apparently wide distribution throughout the world, the total number of cases reported, including the four of Voyles and Beck (1946), seems to be 112, but it is likely that many times this number of cases have gone unrecognized. In most of the cases infection has involved primarily the brain

cutaneous, joint, Hodgkin's-like, pulmonary and other visceral involvements; Robertson *et al.* (1939) very pertinently pointed out that an entity which can simulate a great many other maladies is worthy of more than passing interest to any practitioner. Tinney and Schmidt (1944) reported the ninth case in which there was generalized visceral involvement. The fungus has been isolated from nature and animals but there have been no reports of a natural infection or of transmission from animal to man. Mider *et al.* (1947) reported a case in which there was a mixed infection of both cryptococcosis and histoplasmosis.

THERAPY

The pathogenicity of *C. neoformans* seems to be relatively low until the central nervous system is involved and then the prognosis becomes immediately and absolutely bad; a few cases are recorded, however, in which self-arrest

nevertheless justifiable since complete inhibition of growth *in vitro* can be

were not truly maduromycosis, there is on the other hand a great likelihood [illegible] the past under the [illegible] ...ost frequently in a barefooted person, and practically always in a rural area. Following an incubation period thought to be between two weeks and three months, the fungus grows within the deep tissues and causes necrosis which eventually reaches the surface. The typical lesion is a deep sinus that is discharging a foul-smelling oily fluid containing certain characteristic grains. The whole foot may be riddled with a network of intercommunicating sinuses of this sort and is much swollen and characteristically deformed. Pain is usually of a dull aching sort and constitutional symptoms are slight and inconstant. The disease may last many years; there is no tendency to heal.

THERAPY

Amputation seems to be the only treatment of established value since local measures are of no avail and internal medication with the iodides, thymol, copper sulfate and all the other agents usually tried in fungus infections has always failed to alter the lesions. I think I should add, however, that Dixon (1941) successfully used sulfanilamide internally in a case that had the physical characteristics and clinical course of maduromycosis, though the attempt to culture the fungus was unsuccessful; and that, because of the great similarity in the clinical picture of cases of madura foot caused by Actinomyces and those caused by true fungi, Peters (1945) recommended full sulfonamide dosage for three weeks in all cases before advising amputation, for he had excellent results in an Actinomyces case seen here in the United States. However, in [illegible] Twining *et al.* (1946), on th [illegible] unable to say that penicillin [illegible] symptoms of the disease in a prompt and spectacular manner. In one case, although the lesions at the final admission to the hospital remained uninfluenced, pain was completely relieved; amputation had finally to be resorted to in this case. In the second case, in which only the soft tissues were involved and hence the picture was not entirely classical, at the end of eight months after penicillin treatment the "cure" appeared to be permanent.

MONILIASIS

In some of the intertriginous infections of the axillae, the inguinal region and the infra-mammary areas, in some cases of vulvovaginitis and sometimes in perlèche, and in some cases of paronychia, the fungus *Candida* (*Monilia*) *albicans* can be recovered. It is also the causative organism in the type of stomatitis known as thrush, which is dealt with elsewhere in the book. Sometimes this agent is also the causative organism in a bronchopulmonary moniliasis characterized by cough, normal or slightly elevated temperature, scanty mucoid or gelatinous sputum containing small gray flakes of fungus cells and detritus, and an intermittent course during many years in which the patients's health is usually not seriously affected. It is said that an unusual type of bronchopulmonary moniliasis affects the teatasters in Ceylon. The more severe pulmonary moniliasis, in which there occurs extensive invasion of the lungs, is oftentimes practically indistinguishable from pulmonary tuberculosis. Blood stream invasions sometimes occur,

in four such cases recorded in the literature the organism was identified as *C. parakrusei* and in the fifth as *C. guilliermondi*. These cases all ended fatally, but Wessler and Browne (1945) reported a case in which the organism isolated was *C. albicans* and in which at least temporary remission occurred. Meningeal involvement due to *C. albicans* has been rarely described, but Morris *et al.* (1945), and Halpert and Wilkins (1946), have each recently reported a fatal case of meningitis in which this organism was implicated in the causative role. Duncan (1945) cited three cases of acute mycotic otitis in which it seemed likely, in line with the *in vitro* findings of Keeney *et al.* (1944), that the clearing up of the staphylococcal otitis media by local application of penicillin served to stimulate the *Candida* to greater activity.

THERAPY

Smith (1945) said that bronchopulmonary moniliasis can usually be cured ... ases often ... at intra- ... or every other day, for four to six doses sometimes results in dramatic improvement in patients who do not respond to the iodides. Vaccines must be employed for ... the ... by ... no ... cultures twenty-four hours after their use was begun, the cultures remaining sterile throughout the subsequent period of time that the case was under observation. In the severe case of pulmonary moniliasis of Hiatt and Martin (1946), in which the iodides could not be used because of extreme sensitivity to them and the use of gentian violet therapy had to be discontinued because ... taneously, beginning with 0.1 cc. of a 1:10 dilution and increasing by 0.1 cc. daily until a dose of 0 9 cc. was reached Following this therapy, the series of injections being repeated twice, there was a total remission of all subjective symptoms and x-ray study of the chest showed what was said to be remarkable clearing, the patient being discharged feeling well and entirely symptom-free, x-ray studies of the chest two months later were interpreted as essentially normal

PULMONARY ASPERGILLOSIS

Primary pulmonary aspergillosis is very difficult to diagnose before death because the symptoms and physical findings are practically indistinguishable from those of chronic pulmonary tuberculosis However, Smith (1945) said that if the patient develops marked sensitivity to the antigens of the organism both the clinical course and the appearance of the shadows in the ... ported fairly widely throughout the world. An interesting feature of th disease is that it occurs most often in those exposed to massive doses

probably the chief reservoir and chief transporting agent of the causative organism. One thing is certain, that if a stranger leaves the endemic valley while it is still daylight he is almost sure not to contract the disease since these sandflies are night feeders. The incubation period is from two to three or more weeks; it was twenty-one days in the experimental infection of the young student, Carrión, who died a martyr to his investigations. The studies of Howe (1943) made it appear unlikely that agglutinins play any major part in the almost universal acquired immunity which follows a typical attack of the

the parasites present in the red blood corpuscles. Weinman (1946) said that the physical examination is not very revealing, the most characteristic finding being generalized enlargement of the lymph nodes. The mortality is variously estimated at from 40 to 80 per cent, but as many of these patients are affected with other chronic tropical diseases at the same time it is perhaps unfair to ascribe all the deaths to uncomplicated Oroya fever. The fatal cases run their course in a few weeks; it seems that most of those who survive Oroya fever ...h.

...isease, which may occur without a ...acterized in the beginning by joint pains and a moderate fever of short duration, after which the eruption appears This eruption is at first miliary and is usually confined to the arms and legs, but it may occur elsewhere on the body and even on the mucous membranes. In most cases the rash becomes papular and subcutaneous nodules appear. Weinman (1946) said that the patient appears as though he had been studded over with innumerable cranberries varying in color from red to purple. Some of these nodules, attaching to the skin and ulcerating, are called "verrugas" and have given the disease its name. The eruption persists from one month to two years, but individuals who are not harboring other malicious tropical diseases at the same time nearly always recover; it seems, however, that in rare instances Oroya fever may carry off the patient after he has survived verruga Only the ulcerated lesions leave any scars Fox (1935) described the dermatologic lesions in detail

THERAPY

...and the interest it has ...levised, ...lin cer- ...herapy. Strong (1940) said that it was the consensus among conservative physicians in Peru that the arsenic-antimony compound, Sdt. 386 B, which was said by Kikuth (1937) to have been used successfully, is not of value; Merino (1945) confirmed this viewpoint. Patino-Carmargo (1939), Groot *et al.* (1942), Merino (1945), and Hodgson (1947), have mentioned such agents as vitamins, calcium, antimony, arsenic, iodine, quinine, quinacrine, sulfonamides. liver extract, blood transfusion, autohemotherapy, etc—the usual list of agents when specific therapy is not at hand. Howe (1943) produced immune serum of high agglutinin titer in rabbits and injected three patients with severe Oroya

fever with this serum but without dramatic therapeutic effects The studies of Howe and Hertig (1943) indicated that vaccination with preparations of formolized suspensions of *B bacilliformis* might definitely ameliorate the course of potentially serious cases though it seemed unable to prevent the development of the disease

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PLAGUE

[illegible]

province of public health authorities or other specialists of great experience.

PNEUMONIA (TYPICAL)

While recognizing that the differentiation between lobar and bronchopneumonia is not always easy, indeed sometimes impossible, to make at the bedside, [illegible]

potentially dangerous of all the infectious diseases of the temperate zones. Appelbaum and Shrager (1945), in reviewing the subject of the pneumonias in Panama, seemed to feel that the alleged rarity of pneumonia in the tropics is largely due to the fact that studies have been more extensive, facilities more accessible, and reports in the literature more abundant in the temperate zone; certainly Mumford and Mohr (1944) reported a high incidence of pneumonia in the native populations throughout all of the Southwest Pacific area In about 90 per cent of instances the disease is caused by *Diplococcus pneumoniae*, in [illegible]

stances the physical findings are not entirely typical of the lobar form of the disease Dubin and Kerby (1943) described a case of pneumonia studied at autopsy in which it seemed reasonably certain that the etiologic agent was *Escherichia coli* Levine and Plattner (1944) described three cases in which pneumonia was diagnosed before *Salmonella suipestifer* was isolated from the [illegible]

organism present in the mouth of most individuals is not the one responsible for most cases of the disease, present knowledge inclines toward the position that [illegible]

in the community. Recent head cold or grippe, exposure to wet and cold, and excessive fatigue are frequent precursors of the disease; the incidence is decidedly higher among blacks than whites.

Average pneumonia mortality before the advent of effective chemotherapy was: private practice, 15 (!) to 25 per cent; good general hospitals, 25 to 35 per cent, public institutions treating the lowest classes, including many alcoholics, 50 to 60 per cent. In general the mortality trend has been downward throughout the world during a long period of years much antedating specific therapy, and now that we have the new drugs it is exceedingly low—Morgan (1944) reported the astonishingly low figure of 0.7 per cent in the soldier population during War II, a figure probably reflecting as much as anything the fact that nowadays the specific drugs are used before most of the pneumonias really get started However, in spite of the modern chemotherapeutic agents, employed with the utmost skill, pneumonia will still carry off some patients in the older age groups, some with severe complications, and some in whom for one reason or another the treatment is begun very late. In a series of ninety-four patients treated by Dowling *et al* (1946) with penicillin and sulfadiazine there were four deaths, one patient was admitted in delirium tremens on the ninth day of disease and died of empyema that may have been present before treatment was begun and may have developed during the treatment; two were in the older age groups, one being eighty years of age and the other sixty-one, the latter also suffering from congestive heart failure and being a chronic alcoholic; and the remaining patient was admitted in a moribund condition and died six hours after treatment was initiated. In Zeman and Wallach's (1946) 166 patients sixty years of age and older, mortality was 20 per cent despite the expert employment of the sulfonamides, penicillin and even in a few instances type specific serum

In lobar pneumonia the incubation period is generally thought to be from two to seven days; in the case of Hall (1945), precisely eighty hours ($3\frac{1}{4}$ days) elapsed between exposure and the initial rigor. Lobar pneumonia is often but not invariably characterized by the suddenness of its onset, typically with a chill, stabbing pain in the side, high rise of temperature and pulse rate, rapid respiration often with dyspnea, cough and rusty sputum, and involvement of the nervous system ranging from mere anxiety to active delirium. Herpes simplex, jaundice (possibly of more frequent occurrence in Negroes than in whites and likely due in them, in the opinion of Turner *et al.*, 1943, to improper nutrition) and initial vomiting are often seen. There are typical physical "findings" in the chest, whose description has no place here. Thomson *et al.* (1946) showed that deviations from normal are frequently found in electrocardiographic tracings taken during pneumococcus pneumonia Cyanosis, varying in degree with the respiratory and circulatory involvement, always makes its appearance later. In the average case, if not treated by the newer specific methods, the symptoms last for from five to ten days with very little remission and then the attack terminates by a gradual lessening in severity of all symptoms or, in less than half the cases, by a "crisis" in which the defervescence occurs within twenty-four hours.

Bronchopneumonia.—Bronchopneumonia is a diffuse lobular inflammation of the lungs in which several organisms can be identified as the causative factor. There are several types:

(1) Primary bronchopneumonia, occurring in children under four years of age. This type is not directly associated with any other disease, is usually mild,

and is nearly always caused by the pneumococcus; the symptoms are much like those of lobar pneumonia except for the difference in the distribution of the pulmonary lesions.

(2) Secondary bronchopneumonia is caused by staphylococcus, streptococcus, Pfeiffer's bacillus (*Hemophilus influenzae*), sometimes Friedlander's

pneumococcus, streptococcus and staphylococcus Secondary bronchopneumonia is the most dreaded complication of the infectious diseases in children and of the infectious and chronic debilitating diseases of middle and old age; many postoperative pneumonias and some post-traumatic pneumonias are of this type. The symptomatology of bronchopneumonia is too diverse and complicated to warrant description here; suffice it to say that the occurrence of this complication is usually marked by a change in the severity and finally the type of the symptoms, until ultimately the respiratory and circulatory embarrassment, cyanosis, general toxemia and diffuse chest involvement of bronchopneumonia completely overshadow or supersede the original picture.

(3) Primary epidemic bronchopneumonia The mortality is very great in these cases, as witness the epidemic during the first World War. Most of the postinfluenzal pneumonias of that dark period were caused by *Streptococcus hemolyticus*, with or without the accompaniment of other organisms whose virulence had been temporarily raised to a high pitch, but in more recent influenza epidemics the staphylococcus has also appeared as a complicating organism

medicated liquid petrolatum drops or sprays intranasally over a long period of

tionally exposed In Sodeman and Stuart's (1946) review of adult cases of lipoid pneumonia they emphasized how easily confusion may occur with bronchiectasis, tuberculosis, primary and secondary malignancy, pulmonary infarction, acute bronchopneumonia, unresolved pneumonia, fungus infections and pneumoconiosis There is no roentgenologic picture that, in itself, is diagnostic of lipoid pneumonia

In the aged, pneumonia is many times not clear-cut in type; the onset may be insidious and the course, which is sometimes even feverless, may be very protracted, high incidence of pre-existing circulatory and renal disease of course much increases the gravity of the situation.

CHEMOTHERAPY

Under sulfadiazine or penicillin in the vast majority of pneumonias the temperature curve turns sharply downward, often reaching normal within or *before* twenty-four hours and practically *always* under forty-eight hours; indeed if fever continues beyond forty-eight hours it is usually found that there is some serious complication or the pneumonia is of a rare unresponsive type. The respiratory and pulse rates and the leukocyte count also decline and the

patient ceases to give the impression of one critically ill, but nevertheless he does not often show that striking change characteristic of normal unaided crisis, *i.e.*, the physical signs may persist or even continue to develop for a time. Complications are certainly being seen much less frequently in this new chemotherapeutic era, but in the nature of things we shall probably not ever be able to prove the point sharply with statistical evidence. Two points, made by leaders in this field some years ago, are worth reemphasizing here: one is that we are likely nowadays to lose track somewhat of the prevailing types and severity of pneumonia because so many unrecorded cases are being treated in the home, and the other is that we may be seeing sequelae heretofore unknown because the patients who might have developed them in an earlier day all died. Strauss and Finland (1942) found that recurrences are not more frequent in patients treated with sulfonamides than in those not so treated but that there is a tendency in the drug-treated cases for second attacks to occur with the same type of organism and at shorter intervals; I have seen no statement concerning penicillin in this regard.

Apparent Superiority of Penicillin to Sulfadiazine.—In their comparative trial of these two agents, Anderson and Ferguson (1945) eliminated young adults, who are known to respond excellently to chemotherapy, and chose for their patients males over the age of thirty-five, allocating them in the order of their admission alternately to two treatment groups. There were sixty-three patients in each group, all received the same symptomatic treatment and general clinical control, and the distribution of factors known to influence the course of the disease was uniform. About the same results were achieved with sulfonamides and penicillin, though it seemed that in three patients the latter agent produced an unexpected recovery. And that is about the essence of average clinical experience; *i.e.*, recoveries at times occur with penicillin under circumstances in which the result might not have been so happy with sulfadiazine. In addition, there are certain other factors on the credit side for penicillin. For example, well substantiated instances of penicillin resistance acquired during therapy have not occurred save in rare staphylococcal cases, whereas, according to Kinsman *et al.* (1945), sulfonamide-resistant strains occur in 2 to 6 per cent of pneumococcus cases alone. Sulfonamide-resistant pneumococci usually succumb to penicillin but the reverse is not always true: Tillett *et al.* (1945) had three sulfonamide-resistant pneumococcal cases in which the response to penicillin was prompt, but in seven of eight cases in which there had been no appreciable response to penicillin there was no response to the subsequent administration of sulfadiazine. Lueck and Edge (1945), in 589 cases of penicillin-treated lobar and bronchopneumonia, found that when delay in the use of penicillin was incurred by the prior use of a sulfonamide larger doses of penicillin were needed and more failures were encountered. Then there is the fact, emphasized by Ory *et al.* (1946) that pneumococci are cleared from the sputum more rapidly by penicillin than by sulfonamides. The relative lack of toxicity is of course a great advantage of penicillin, and nowadays the newer administration technics have made the employment of the agent not at all the ordeal it used to be. Meads *et al.* (1945) considered one of the especial advantages of penicillin to be the lack of necessity for administration with it of alkalis in large amounts of fluid, thus escaping the occasional case of serious water retention associated with sulfonamide administration. And finally there is the list of instances in which penicillin administration is mandatory: in pa-

tients known to have been sensitized to sulfonamides; in patients in whom a sulfonamide has not lowered the temperature and effected clinical improvement in about thirty hours; in patients who develop serious reactions to the sulfonamides, in patients who have an initial leukopenia; in patients in whom a complication or coexistent disease hampers urinary excretion of the sulfonamide.

Anderson and Ferguson (1945) found that the complication of delayed resolution occurs just as frequently following penicillin as following the sulfonamides, and they felt that the frequent occurrence of slow resolution with these modern therapeutic agents is the price we must pay for stopping an infective process too quickly.

It would seem that the extensive experience with the sulfonamides that has now been had has established sulfadiazine as the drug of choice in the treatment of pneumonia because of its greater efficacy and lower toxicity. However, Flippin *et al.* (1943), Genecin *et al* (1945), and Thompson and Blankenhorn (1946) have reported very favorably upon sulfamerazine, Ruegsegger *et al* (1943) on sulfapyrazine, and Loughlin *et al.* (1944) and Melton (1944) on sulfamethazine.

Penicillin Administration.—This matter is fully discussed in the article on Sepsis (*q v.*).

Sulfadiazine Administration.—In 1944, a Pneumonia Advisory Committee to the Department of Health of New York City stated that the accepted dosage schedule for sulfadiazine consists of an initial dose by mouth of 60 grains (4 gm.) followed by 15 grains (1 gm.) every four hours until the symptoms have subsided and the temperature has been normal for forty-eight hours Where patients are seriously ill, or in the presence of vomiting, it was felt desirable to substitute for the initial oral dose an intravenous dose consisting of 75 grains (5 gm) of the sodium salt of sulfadiazine dissolved in a liter of physiological saline solution, or 500 cc of 1/6 molar sodium lactate

to maintain an alkaline reaction of the urine, for the latter purpose 90 grains (6 gm) of sodium bicarbonate have been recommended as an initial dose and 40 grains (2 5 gm.) of the same agent every four hours as the continuation dosage for adults. Penna and Christopher (1946) determined that 15 gm of sodium bicarbonate daily, given intravenously in two doses each of 7.5 gm in 100 cc. of water twelve hours apart, will keep the urine sufficiently alkaline to prevent sulfadiazine crystalluria in the average adult; they said that the same degree of alkalinization can be obtained with one-fifth the volume of solution that is necessary when 1/6 molar sodium lactate is used. If the patient has a complicating nephritis or congestive heart failure the situation is of course a difficult one because the sodium ion promotes fluid retention The use of potassium salts by mouth would be theoretically indicated, but Flippin *et al.* (1946) found that potassium bicarbonate was relatively ineffective when compared with sodium salts in lessening the incidence of crystalluria.

of acetylsulfadiazine dissolved, whereas raising the urine from acid to alkaline in reaction will increase its solubility more than twenty-five times.

I think it should be pointed out that there have been departures from the above recommended 4 gm. followed by 1 gm. every four hours schedule, for one finds both higher and lower dosage being employed. In a direct comparison of low with moderately high dosage, Dowling *et al.* (1943) treated eighty-one unselected adults with pneumococcal pneumonia with an initial dose of 30 grains (2 gm.) followed by 7½ grains (0.5 gm.) every four hours until recovery was certain or death ensued, while an alternate group of seventy-nine patients was given 90 grains (6 gm.) initially, followed by 15 grains (1 gm.) every four hours. The higher doses were slightly more often followed by rapid recovery than the lower doses and there was less likelihood of relapse, spread of the pneumonia to another lobe, or of delayed resolution in the patients receiving the higher dosage; nevertheless it was evidenced from this study that the smaller doses could be used without fear of an increase in the mortality rate or of serious complications. Plummer (1944) recommended that, after the initial large dose, 15 grains (1 gm.) be given every four hours but omitting the 4 A.M. or another of the night doses, so that the patient actually obtains only 5 instead of the usual 6 gm. per day. Upon the other hand, there is evidence in favor of higher dosage and also of the routine administration of an initial intravenous dose to all patients who are moderately or severely ill, for it has been found that sulfadiazine is erratically absorbed in sick and toxic individuals. Collen and Phillips (1945) sought to determine optimum dosage during a twenty-month period in which 1465 patients with pneumococcic pneumonia were treated in a civilian hospital. In the first half of the period, 618 consecutive patients were given 5 gm. initially (orally or intravenously as seemed indicated) and 2 gm. every six hours orally thereafter, maintaining an average blood level of 8 to 10 mg. per cent. In the second half of the period, 748 consecutive patients were given double doses, the majority of them receiving 5 gm. of sodium sulfadiazine in 500 cc. of 1/6 molar sodium lactate solution intravenously and 5 gm. of sulfadiazine orally initially, followed by 4 gm. of sulfadiazine orally every six hours thereafter, maintaining average blood concentrations of sulfadiazine from 12 to 20 mg. A comparative analysis of the various important factors influencing the mortality rate in pneumococcic pneumonia, such as age, specific pneumococcic types, incidence of bacteremia, leukopenia, severity of associated diseases, extent of pneumococcic involvement, number of days of illness prior to hospitalization, and incidence of patients admitted who died soon after, was made and it was found that the two groups had pneumococcic pneumonia of comparable severity. Adjuvant therapy, including the use of specific pneumococcus serum, was similar in both groups. The results of this study showed that in the patients receiving double doses of sulfadiazine there was (a) a decrease in the gross mortality from 10.7 to 6.2 per cent (corrected for patients dying in six hours after hospitalization, the mortality rate decreased from 10.2 to 5.5 per cent); (b) a decrease in the incidence of sterile pleural effusions from 5.2 to 2.7 per cent; and (c) a decrease in average number of days in the hospital, 66 per cent of the high dose group requiring less than seven days for recovery as compared to 45 per cent of the low dose group. Amazingly, there was no greater incidence of drug toxicity in patients treated with double doses of

sulfadiazine than in those treated with the usual doses, which is a direct contradiction of the finding of Plummer and Wheeler (1944), in a very large scale study, that the incidence of toxic reactions is directly proportionate to daily dosage and total dosage.

Sulfadiazine Dosage for Children.—The rule of thumb dosage for children, as stated by Janeway (1943), is an initial dose of 3/4 grain (45 mg) per pound body weight, and then 1 grain (60 mg) per day per pound divided into four or six doses, whichever is most convenient. Klein (1946), acting upon the observation at the Children's Hospital in Boston that infants treated with sulfonamides and adjuvant alkalis became edematous more often than might have been expected, decided to see whether the edema could be prevented by using alkalis with cations other than the sodium ion. Potassium citrate was chosen because of its high solubility and availability at the time, and without selection alternating admissions requiring sulfonamide therapy were given either sodium bicarbonate or potassium citrate. The dosage of the sodium bicarbonate ranged from 0 28 to 0.42 gm. per kg. and that of the potassium citrate between 0 44 and 0.70 gm. per kg Several mixtures of the two agents were also tried. It seemed possible to conclude from this study that the substitution of alkalis containing the potassium instead of the sodium ion results in a significant lessening of the incidence of edema in association with sulfonamide administration in infants.

Sulfonamide Toxicity, Resistance, Etc.—See the separate chapter on this subject at the end of the book.

Penicillin and Sulfadiazine Together.—Dowling *et al.* (1946) placed alternate patients in two groups of ninety-four patients each, the type distribution of pneumococcus being approximately the same for the two groups. These

tality in the two groups was respectively 9 6 per cent for those treated with sulfadiazine alone and 4.3 per cent for those treated with sulfadiazine plus penicillin, a result which the authors considered not statistically significant but certainly suggestive. The time required for the temperature to fall permanently below 101° F. (38° C.) was strikingly similar for the two groups. No toxic effects were observed from the administration of penicillin, but one patient developed drug fever, two dermatitis, and one gross hematuria with sulfadiazine. Kaske (1946), describing the treatment of 1265 pneumonia cases with no deaths in the Navy, said that when penicillin alone was given the response was not so remarkable as when penicillin and sulfadiazine were used in combination, and furthermore that the earlier penicillin was instituted after sulfadiazine had been administered the more quickly the patients' temperature returned to normal.

Superiority of Penicillin to Serum.—During a period when penicillin was scarce, Collen *et al* (1946) treated a large series of cases of pneumococcic pneumonia routinely with sulfadiazine and supplemented this by the use of penicillin when (a) there was a high pneumococcus sputum count, evidence of impending pulmonary edema or shock, severe toxic delirium, a leukocyte count below 6000 cells per cu. mm, or other evidence of severe

infection or toxicity; (b) failure to respond to adequate dosage of sulfadiazine; (c) the presence of pneumococcus type III pneumonia in patients over forty

cases

was tr

it was

alone was 0, while in the severe cases in which penicillin was also used the mortality was 6.7 per cent, in the other series the mortality under sulfadiazine was 0.7 per cent and under serum plus sulfadiazine 26 9 per cent. It is therefore evident that in the routine treatment of lobar pneumococcic pneumonia with sulfadiazine, supplementation with penicillin in cases of especial severity is far superior to supplementation with serum under the same circumstances.

Streptomycin in Friedlander and Hemophilus Infections.—Several reports have appeared of one or two cases each in which patients infected with *Klebsiella pneumoniae* (Friedländer's bacillus) or with *Hemophilus influenzae* (Pfeiffer's bacillus), who did not respond to penicillin, were successfully treated with streptomycin; but Keefer *et al.* (1946), reporting as the Committee on Chemotherapeutic and Other Agents of the National Research Council, pointed out that it is not uncommon to observe a complete change in the bacteriologic flora of the sputum of patients with pulmonary infec-

tomycin alone was used from the beginning it will be difficult to know just how effective this agent is in these situations.

OXYGEN THERAPY

Unlike serum, which has been completely superseded by the chemotherapeutic agents in pneumonia, oxygen still has a place in the therapy of the relatively small number of cases that do not respond to the drugs, in complicated cases, and in severe cases in which treatment has been begun late. So far as I am aware, there has not been published satisfactory proof that oxygen therapy is lifesaving, though the patient often looks and feels better under its influence; the rationale of its employment lies in the following propositions: (a) proper aeration of the blood is difficult in the normal atmospheric content of oxygen because shallow breathing does not permit full ventilation of the

gastro-intestinal, respiratory, circulatory and central nervous system ... bance. Comroe *et al.* (1945) found that 50 per cent oxygen administered during a twenty-four hour period provoked no symptoms but 75 per cent caused symptoms in 55 per cent of their experimental subjects; these observers felt that 100 per cent oxygen for short periods is probably safe in all patients, but that when oxygen must be given in excess of twelve hours it should not exceed 60 per cent unless this is insufficient to saturate the arterial blood, in which

case careful check must be kept for substernal distress, signs of nose and throat irritation, and decrease in vital capacity during the period in which a higher concentration is being administered.

In place of the completely enveloping tent, which is greatly objected to by many patients and is extremely difficult to operate, numerous hospitals have one or the other of the several types of face mask or hood which have been devised. Each of these has its advocates, of course, and they are probably all fairly satisfactory, but it seems that most oxygen is still administered, whether it be in homes or hospitals, by either the nasal catheter or nasal inhaler methods.

Nasal Catheter Method.—A special nasal catheter may be used but the ordinary urethral soft rubber catheter, No. 10 to 14 French, is just as good provided that several holes are cut in it at intervals of ½ inch. Following the directions of the Committee on Inhalational Therapy of the New York Acad-

pharynx opposite the glottis, a concentration of 42 per cent oxygen may be obtained at a flow of 5 liters a minute, but it should be remembered that oxygen may pass into the stomach and distend the abdomen if the catheter is placed lower than the uvula. The catheter is supported and held in place by bringing it up over the nose and fastening it with adhesive tape to the forehead or cheek. The advantage of using only one catheter at a time is that a fresh one can be introduced into the other nostril before the old one is removed, a fact of great importance in a patient attuned to oxygen concentrations higher than normal; replacement should take place every twelve to twenty-four hours, more often if the quantity of mucus necessitates it

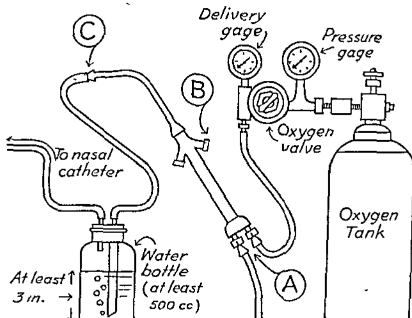
Nasal Inhaler Method.—The inhaler is a metal Y-tube (malleable, so that it can be bent for individual adjustment) with plugs on the two ends of the Y

a given flow rate as with the nasal catheter (see above), children will rarely tolerate a flow of more than 2 liters by either method Even the most cooperative patient often cannot refrain from pulling the inhaler plugs out of place because of the irritation they cause.

Oxygen Supply.—Tanks of commercial oxygen as used by welders are just as satisfactory as and cheaper than so-called "medical" oxygen. The larger the tank the cheaper the unit of oxygen; the "large" 244 cubic foot tank will deliver 6905 liters of gas—enough for nineteen hours at 6 liters per minute. The apparatus in use in hospitals, and available on rental for use in the home

be converted very quickly into a satisfactory machine for the regulated delivery of oxygen to a patient. One should be very careful to keep oil of any sort away from all parts of such an apparatus

DIAGRAM AND TABLE FOR CONVERSION OF OXYACETYLENE WELDER INTO APPARATUS FOR DELIVERY OF THERAPEUTIC OXYGEN



At A disconnect tube from acetylene tank
At B open the valve fully and leave it open.
At C read the standard size number of the welding tip
Apply to the Table to learn what the oxygen delivery gauge must read for each size welding tip in order to deliver the desired number of liters per minute to the patient.

Pounds pressure shown on delivery gauge.	Liters of oxygen delivered through welding tips *				
	No 1.	No. 2	No. 3.	No. 4.	No 5.
2	2	2 25	3 25	3 75	4
3	3	3 5	5	5	6
4	3 75	4 25	6	6	7
5	4	5	6 75	7 5	8
6	4 5	5 5	7 75	8	9
7	5 25	6	9	9	10
8	5 75	6 5	9 75	10	11

* I am very grateful to my former technician, the late Oscar Ugi, who derived these figures for me

NURSING MEASURES

The patient should be put to bed in a well-ventilated room and in severe cases the use of the bedpan and urinal should of course be enforced. But having thus conserved the patient's strength it is doubtfully advisable to waste it again by permitting him to move about very much in order to facilitate the percussion and auscultation of his back. If the mouth is kept clean the patient will be more comfortable than when it is dry and dirty and he will also eat and drink with more relish, possibly, too, the danger of superinfection may be lessened. The best way to keep the mouth clean is to wash it with alkaline

sacred nursing ritual may be highly advisable on the worst days in the rare patient who has not responded well to one of the specific agents. As a matter of fact the sole reason for giving this bath is to cleanse and refresh the patient. If it tires and irritates him, as is very often the case when it is combined with a bustling bed-changing bout, why persist in it? No one has yet died from lying in bed for a few days without a bath or a stem-to-stern change of linens Nowadays the initiation of disturbances of the nervous system through hyperpyrexia is very rarely seen, but when it is encountered the antipyretic drugs will control it much more safely than rigorous cold bathing procedures I like very much Hall's (1936) reminding us of the old soldier's notice, pinned on the bed, "Too sick to be nussed today."

And when the corner has been turned? Two weeks in bed after the temperature is permanently normal, and a very gradual resumption of accustomed activities I am aware that the new specific agents are "getting 'em out earlier," but I still think that a bit of a coddling period, particularly for those in or past

DIETETICS, FLUID AND CHLORIDE ADMINISTRATION

The course of an attack of pneumonia being usually only a few days, there is no need to worry if the patient's total caloric intake falls somewhat below the

too much sweetening. The following *mixture (which I present as a formula)* enabled Wilder and Drake *to give chlorides, fruit juice,* dextrose and water all in one drink:

Sodium chloride	1 gm.
Dextrose	30 gm.
Orange juice	200 cc
Water	400 cc

In the dietary outline which follows, the patient will *obtain 50 gm. of protein* and 1800 or more calories, the latter depending upon what additional *amount of* fruit juice (or of the above mixture) he will care to take:

[illegible]

and egg was previously taken).
8 P.M. A glass of milk or buttermilk.

Fruit juice may be given several times during the night; it should be presented with some persuasion at least twice if the patient is awake. The very ill *patient is not to feed himself* but is to use a glass tube for the liquids and the semisolids are to be spoonfed by the nurse. The subsequent return to the normal diet should be made by adding buttered toast and small servings of puréed *vegetables, chicken, or red meat and potato to the above diet.*

SYMPTOMATIC TREATMENT

Cough.—*Though this is a beneficent measure, designed to rid* the bronchi of foreign material which is choking them, it is sometimes excessive. Whenever cough is in the least degree exhausting the patient, attempt should be made to control it by such measures as have been described in the discussion of the Common Cold (see Index).

Pain.—The pain in the side is often satisfactorily controlled by judicious employment of adhesive plaster and a hot-water bag, occasionally an ice-bag will give more relief but it should probably not be applied more than two hours consecutively. If the pain is very severe and causing considerable restlessness, only the opiates will give relief. Codeine, 1 grain (60 mg.), may suffice; if not, morphine $\frac{1}{8}$ to $\frac{1}{4}$ grain (8 to 15 mg.), or dilaudid, 1/50 to 1/30 grain (1.2 to 2.0 mg.), may be given but the single dose perhaps had best not be repeated because of the possibility of increasing abdominal distention and decreasing pulmonary aeration. Sometimes also the patient becomes quite ill, even to the point of vomiting several times, a few hours after taking morphine, perhaps more rarely after dilaudid. Some men feel that opiates should never be employed in pneumonia, the controversy is a very old one.

Diathermy sometimes induces great relief, and it is now the consensus that it has no effect other than that; Reimann (1939) said that in his experience a *hot sandbag or water bottle provides just as much comfort at much less cost.* Schnur (1939) sought to relieve pleural pain by local injection of procaine (novocaine), infiltrating 5 to 10 cc. of 2 per cent solution intracutaneously, subcutaneously and into the region of the pleura, most of it being injected

deeply; immediate relief was obtained in all thirty-two cases and in twenty-one of them the relief was permanent. Artificial pneumothorax will also relieve pain but of course such a radical measure is rarely resorted to nowadays.

Restlessness and Delirium.—Restlessness and sleeplessness must be overcome since peace of mind and body are of considerable importance to the patient. Certainly no one can cavil at the statement that it is well to try a milder sedative before resorting to an opiate in order to secure bodily quiet Delirium may appear very suddenly, even in a patient who has not been previously restless, and cause such violent exertion as to induce sudden death. Bullowa (1933) reported the satisfactory use of avertin in these cases, 60 mg. (1 grain) per kilogram (2.2 pounds) by rectum. When the patient was very violent and rejected much of the drug he used a barbiturate in addition—5 mg. (1/12 grain) of dial-with-urethane per kilogram (2 2 pounds), intramuscularly or intravenously. The study of King and Moersch (1941) indicated that there is no danger in using the barbiturates in ordinary sedative dosage when the sulfonamides are being employed

Tympanites.—Distention of the abdomen with gas is a symptom that is distressing and serious for it oftentimes adds to the respiratory embarrass- [illegible]

enema as soon as the case comes under observation. In the opinion of many men this enema should be repeated at least every twenty-four hours, a rectal tube being used during the interim, others give ½ to 1 ounce (15 to 30 cc) of liquid petrolatum every night and an enema only if needed because of distention When distention is severe and persistent, turpentine stupes may be employed as in the following method.

First place a blanket under the patient in such manner that it can be drawn across the abdomen in "double-breasted" fashion. Anoint the abdomen with petrolatum. Then spread a Turkish towel over a small pan and place in the center of it another Turkish towel folded to the size of the abdomen. Now pour over this second towel boiling water, to which has been added 1 teaspoonful of turpentine to the quart, take up the two ends of the first towel, and quickly wring the stupe nearly dry by twisting these ends in opposite directions. Then remove this stupe, which is so hot that you can only hold it by rapidly shifting hands, from the wringing towel and place it upon the abdomen—and lift and replace, lift and replace, until the patient can bear the heat; then draw a layer of the blanket tightly across the abdomen from each side—and you have done it! The stupes must be applied every five minutes until relief is obtained, and in addition ½ to 1 cc of pituitrin or pitressin may be given every twenty minutes for 2 or 3 doses.

The following carminative enemas may sometimes be useful: (1) ½ to 1 drachm (2–4 cc) of turpentine, emulsified by beating with the white of an egg, and added to a quart of water. (2) One to 3 drachms (4–12 cc.) of the emulsion of asafetida added to a quart of water, this latter preparation is esthetically very objectionable

When dilatation of the stomach occurs the situation is indeed serious, though some men attempt to introduce a Levine tube or to employ the Wangensteen suction apparatus.

Circulatory Disturbances.—In many cases of pneumonia of moderate severity the pulse is no more rapid throughout than is consonant with the ele-

vation of temperature. Also it not infrequently occurs in fatal cases that the failure seems to be entirely respiratory, pulse rate and force remaining quite good almost to the end. Again, we have to date no blood *pressure studies which* can be accepted as proof positive that early primary circulatory failure is *typical* of this disease. However, it is undeniably true that there is some degree of circulatory failure in most cases and that in many fatal instances the death seems to be primarily a circulatory one. We now know definitely that this failure is a peripheral circulatory one, though the mechanism of the vasodilation is not yet understood. Therefore, since it is peripheral vascular relaxation rather than heart failure with which we have to deal the situation is a very serious one indeed, for we have no drugs that are really satisfactory aids in such a situation. The Cornell and Rockefeller Institute groups conclusively showed many years ago that digitalis is *not indicated; indeed, should auricular* fibrillation supervene and necessitate the use of the drug it should be employed in dosage considerably lower than would routinely be used in such cases. Caffeine, metrazol, coramine, strychnine? They have all been tried and without much success. Eggleston (1941) considered adrenalin to be contraindicated. Rich (1944), and others before him, suggested that such circulatory failure as occurs in pneumonia might be due to adrenal insufficiency; indeed, Perla and Marmorston (1940) felt that satisfactory results were obtained by the use of

of chemotherapy, Underhill and Ringer studied a series of forty-three cases of influenzal pneumonia from the standpoint of blood concentration, and were able to show a distinct relationship between the gravity of a given case and the extent of the abnormal concentration of the blood. Upon theoretical grounds they advocated the withdrawal of blood by venesection and the introduction of fluid into the body but were unable to carry out the treatment in many cases. Of course nowadays the indications for this procedure, that was at once the darling of our forefathers' hearts and the object of their greatest therapeutic abuse, rarely arise, but Conner (1941) felt that in some instances of pulmonary edema occurring early in the disease venesection may be justifiably resorted to; Eggleston (1941) agreed.

(b) *Dextrose*.—Since there is no reason to restrict fluids because the sulfonamides or penicillin are being given, intravenous infusions of dextrose solution are holding their own very well in the new chemotherapeutic era. The most obvious advantage of dextrose therapy of course is that, while *supplying fluids, it also makes available* in a short time a large quantity of food material which does not have to undergo preliminary digestive processes.

Pulmonary Edema.—This is often a terminal event and nothing can be done. Sometimes, however, it occurs early in the attack. Venesection (see above) may be performed in these cases or one may give concentrated dextrose solution, as recommended by Bullowa some years ago: 100 to 150 cc of 50 per cent dextrose solution *intravenously* at intervals of several hours, attempting to force the lungs to give up their fluids in order to dilute this concentrated solution. One may attempt to overcome excessive loss of fluid into the urine by giving insulin to help metabolize the dextrose; a little less than 1 unit for each 2 gm. of dextrose, subcutaneously at the close of the

intravenous injection. Barach (1942) felt that the administration of oxygen under positive pressure is indicated in some cases of pulmonary edema in pneumonia because the application of this positive pressure to the external capillary wall opposes the internal hydrostatic pressure in the capillary and thus tends to prevent the oozing outward of serum; but he stated that when pulmonary edema takes place in the presence of peripheral circulatory failure this positive pressure therapy is contraindicated for the reason that it has a retarding effect on the entrance of blood into the right heart.

Anemia and Hypoproteinemia.—Armstrong *et al.* (1945) reported two cases in which severe and progressive anemia and hypoproteinemia required the administration of large amounts of whole blood and plasma in order to

severe infections which would otherwise be rapidly fatal.

PROPHYLAXIS

The studies of Joint Commissions from the Office of the Surgeon General, United States Army, and the Office of the Air Surgeon during War II, reported by MacLeod *et al.* (1945), and Hodges and MacLeod (1946), seemed amply to verify the hypothesis that the two major factors influencing the pneumonia rate are the nonbacterial respiratory disease rate and the carrier rate for infective types of pneumococci. There seems to be little hope of reducing the non-bacterial respiratory disease rate until the nature of the underlying agents, their mode of spread, etc. is better understood, but something very definite can be done in the matter of reduction of the carrier rate for infective types of pneumococci.

First, isolation of cases to reduce case-contact-carriers might have some limited value

Second, since dust has been shown to act as a reservoir for pathogenic types of pneumococci, and therefore potentially is a vehicle for the dissemination of these organisms from man to man, efforts directed toward the control of the content of particulate matter in the air of enclosed crowded spaces might be expected to be of some value

Third, the experience gained with immunization with the capsular poly-

in these studies clearly demonstrated that immunization with these specific capsular polysaccharides is effective in preventing the development of pneumonia due to the types of pneumococcus employed in the immunizing injections; and it further showed that immunization of half of the population against these types greatly reduced the incidence of pneumonia due to these types in the non-immunized subjects. This latter point was proved by the

fact that while the incidence of pneumonia of the specific types used in the injections was but 17.6 per cent of that expected in the controls, the incidence of types XII and IV pneumonia in these controls (*i.e.*, the types against which the immunized had not been protected) was closely similar to the expected rates It is difficult to avoid the conclusion from this that failure of a high pneumonia rate to develop in the non-immunized was due to a low carrier rate for the types against which the immunized had been protected. The time required for the development of immunity following injection of the polysaccharides seemed to be about two weeks in these studies, but under the conditions obtaining the full duration of the immune period could not be determined, though it was apparent that six months could be set as a minimum It is certainly unlikely that employment of the specific polysaccharides will be found generally justifiable in civilian populations in view of the relatively low incidence of pneumococcal pneumonia in civil life, but it may be that for certain particular groups the measure will be an entirely feasible one.

Fourth, sulfadiazine prophylaxis was administered to approximately 600,000 Navy personnel, approximately 300,000 similar personnel acting as controls, during War II. According to Coburn (1945) the incidence of pneumococcal pneumonia was significantly lowered at most Naval stations by this measure, the most effective dosage being 1 gm daily, but Kaske (1946) said that upon reinstitution of the sulfadiazine prophylactic program in many of the camps and activities of the Great Lakes Naval Training Center during the winter of 1944–1945, the pneumonia incidence increased. Of course, the daily dosing of an entire civilian population in this way is utterly unthinkable. To be sure, the employment of the sulfonamides in upper respiratory tract infections before the pneumonic process becomes fully demonstrable is in itself a type of prophylaxis, but there is little to say about this sort of thing except that it is being very much done and probably has contributed considerably toward the decline in the incidence of pneumonia *in* recent years.

PNEUMONIA (ATYPICAL)

Primary atypical pneumonia of unknown etiology, frequently referred to [illegible] only in recent times but is a [illegible] se, it [illegible] War II. A deluge of papers upon this subject has appeared in the literature, *but* I think that the classical study was that performed by Dingle and his associates, acting as a committee to study the matter for the Office of the Surgeon General, and reported in May, 1944. In contradistinction to *influenza and to* pneumococcal pneumonia, the syndrome is characterized by gradual onset, mild symptoms referable to the upper respiratory tract, distressing cough, moderately severe constitutional reactions and a marked disparity between the early radiographic and the late physical findings in the chest. In most instances the patient has been suffering from an upper respiratory infection for days or weeks before he is sufficiently incapacitated to seek medical aid; the physician then finds an incapacitating malaise but rarely great prostration, chilliness often but true chills rather rarely, fever which is usually not very

high, headache especially of a frontal type and often very severe, chest pains, and practically always a dry very distressing paroxysmal cough which later becomes productive but rarely purulent or frankly bloody or indeed even rusty.

In an outbreak of 1862 cases at one of the Army posts, van Ravenswaay *et al* (1944) were able to make careful observations on 297 consecutive cases and [illegible]

otherwise present. In the rather characteristic radiographic picture usually presented early in the course of the illness by the majority of patients, the first change to be noted, according to Dingle *et al.* (1944), is an increase in the size of the hilar shadow, unilaterally or bilaterally. Perihilar infiltration becomes increasingly apparent in subsequent films and the shadow then extends toward the periphery in the shape of a fan or wedge, usually fading into the normal lung parenchyma but occasionally extending to the periphery The infiltration is rarely of sufficient density to resemble that of pneumococcal pneumonia, and the process often appears confined to a local area and may spread within a lobe or to an adjoining lobe, but scattered discrete lesions throughout the lung fields are usually not observed Painton *et al* (1946) pointed out that the veil-like extension of the shadows from the hilus or the cloudy mottling with typical lack of homogeneity often makes it difficult to delineate actual lobar involvement

Neither sputum examinations nor blood cultures offer diagnostic aid, and the white and differential blood counts are not very helpful; Meyer and Thewlis (1944) recorded the following findings in fifty cases the leukocyte count was usually normal, the neutrophils and monocytes increased, the lymphocytes decreased, and in about one-fourth of the cases there was eosinophilia after the disease was somewhat advanced Finland *et al.* (1945), who first noted the development of significant titers of cold agglutinins in atypical pneumonia, more recently carried out studies in 1069 cases including normal persons and patients with a variety of conditions, mostly respiratory tract infections of various sorts. Cold agglutinins in titers of 40 or higher were found in 68 per cent of 200 characteristic cases of atypical pneumonia of unknown etiology, in 5 of 11 cases in which this was the probable diagnosis, and in 4 of 7 cases of [illegible]

ceed the highest titer in normal controls and in persons with a variety of acute infections. Adams *et al.* (1946) found a positive heterophil antibody reaction sufficiently often to stimulate their interest in further investigation of this matter. Van Ravenswaay *et al.* (1944) found that in the acute stage of the disease the sedimentation rate is invariably elevated, ranging from 20 to 40 mm per hour, and that it returns gradually to normal as the patient improves; they felt that by the routine use of sedimentation tests it was possible to follow the progress of the cases as satisfactorily as by the routine use of periodic chest plates.

Serious complications occur very rarely in atypical pneumonia and in most outbreaks the death rate has been extremely low; in the 1862 cases of van Ravenswaay *et al.* mortality was only 0.26 per cent even when they included three cases in which death very probably should not have been attributed to the pneumonia; in the series of 480 cases reported by Higley *et al.* (1944), complications of various types were found in 43 per cent but only three patients died because of complications. In the 321 cases of Painton *et al.* (1946), complications of any sort developed in only 7 per cent; the incidence of electrocardiographic changes suggestive of pericarditis or myocarditis in this series was exceedingly low. In reviewing the literature and reporting cases of his own, Holmes (1947) concluded that the nervous system is rarely involved and that when such involvement does occur the tendency is toward complete recovery without sequelae. The febrile course in a case of average severity usually does not extend beyond a week, but there are not infrequently recurrences, or perhaps more correctly reactivations, for the pulmonary process seems to be of a relatively chronic nature, and therefore the period of convalescence is usually protracted. In the few fatal cases that have been investigated, the findings have been principally those of a patchy, hemorrhagic, interstitial bronchopneumonia associated with acute bronchitis or bronchiolitis; but Needles and Gilbert (1944), in reporting one of the autopsies, pointed out what they considered to be the striking similarity of the anatomic changes in this disease to those reported during the pandemic of influenza in 1918 and 1919.

In a few cases of apparently characteristic atypical pneumonia the following diagnoses have ultimately been made: influenza of either the A or B type asso-

monary tuberculosis. But in the vast majority of instances the entity has not been identifiable with any of these diseases and it has to be accepted as a distinctive if not precisely new malady of cause unknown. The extensive studies reported by Dingle *et al.* (1946) as The Commission on Acute Respiratory Diseases indicated that the causative agent is filtrable and that the disease

illnesses occurring in their volunteers who were inoculated with material from the throat washings and sputum of patients ill with atypical pneumonia, but according to Curnen (1946) approximately 50 per cent of patients with primary atypical pneumonia develop agglutinins for this streptococcus whereas in

normal persons or patients with other diseases such antibodies are found in 5 per cent or less. Thomas *et al.* (1945), who comprise the group, including Curnen, working with the M. G streptococcus at the Rockefeller Institute,

days or more, which means very probably that there is some epidemiologic factor which has not as yet been taken into account The occurrence of mild respiratory infections in many of the inoculated volunteers in association

perhaps influenza. One can easily agree with Racker *et al.* (1945) in their recommendation that every effort be made in cases of primary atypical pneumonia, particularly where its occurrence is sporadic, to rout out the pneumococcus as a possible etiologic agent or a secondary invader before denying the patient specific therapy During an epidemic all age groups from childhood to advanced age, regardless of sex and race, seem to be susceptible.

THERAPY

In the present state of our knowledge the treatment is obliged to remain expectant and symptomatic since none of the specific chemotherapeutic agents have been successfully employed. Many observers have found the sulfonamides ineffective, and in fact Dingle *et al.* (1944) felt that their patients were more uncomfortable when receiving these drugs. Keefer *et al.* (1943), Lyons (1943), and Allison (1945) reported the unsuccessful use of penicillin. It is probably well not to employ the salicylates because of the sweating manifested by many of these patients. Roentgen therapy was reported as having been very successfully employed by Correl and Cowan (1943), but this seems not to have come to much. Convalescent serum and pooled normal adult serum, as well as plasma and whole blood from convalescent donors, have been used with both favorable and unfavorable results, probably indicating that not much is to be expected from this type of therapy. In an attempt to determine the optimum period of bed rest that should be enforced, van Ravenswaay *et al.* (1944) made a controlled study of 384 cases divided into two groups, the members of one group were allowed to become ambulatory if they chose after they had been free from fever

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prolonged bed rest the percentage of recurrences was 2.6 and in the other group it was 23.3; members of the "bed rest" group were hospitalized only for 33.5 days as compared to 41.5 days for those in the "ambulatory" group This study would seem to leave no doubt of the advisability of an enforced period of bed rest of two weeks after disappearance of fever in all cases. These observers also found that it was unnecessary to wait until x-ray and physical findings had completely cleared before beginning physical reconditioning in patients who had been afebrile for fourteen days. Kay (1945),

however, would have bed rest continued until all evidences of pulmonary infection have been cleared for he had seen some cases of bronchiectasis, empyema and residual ulcerative tracheobronchitis following a protracted course of atypical pneumonia.

POLIOMYELITIS

(*Acute Anterior Poliomyelitis, Infantile Paralysis*)

Poliomyelitis is an acute infectious disease that typically attacks young children in the summer and early autumn, those under six years of age usually being in the most susceptible group though infants under six months are very infrequently attacked. However, in an unusually severe epidemic of about 600 frank cases, giving an overall rate of 288.6 per 100,000 population in a certain district in New York State, Conway and Bigwood (1946) reported that most cases occurred at seven years, with more cases in the ten- to fifteen-year age group than in those under five years. Adult cases are reported less rarely now than formerly. The causative organism, a filtrable virus, seems to go through avirulent and virulent periods, during both of which many mild, so-called "abortive" cases occur in which there is little or no paralysis, though immunity is conferred by such an attack; during the more virulent periods the disease tends to become epidemic—pandemic, too, at least to the extent that a large number of local epidemics may occur at about the same time scattered throughout the world. Moore and Kessel (1943) presented the hypothesis that poliomyelitis is primarily a disease of extracentral tissues with the seasonal incidence of paralytic complications

to recover the virus from fruit washings. Of course the fact must not be overlooked that such seasonal periods may merely coincide with the height of activity of some hitherto unsuspected or at least unconvicted insect vector The simultaneous occurrence of infantile paralysis in man and of paralytic disease in poultry has been recorded by several observers, chiefly students of the disease in the Argentine. Gordon (1945) found that three of thirty-seven dog serums, collected following the 1943 epidemic in Chicago, neutralized poliomyelitis virus; neutralization was not obtained with the serums of two chickens and six pigeons from the immediate vicinity of a case of poliomyelitis. Jungeblut and Dalldorf (1946) concluded that virus-harboring house mice do not function as a source of poliomyelitic infection for man in an urban environment At least one fact is certainly established, namely, that the virus is often recoverable from the stools of patients and of healthy contacts and from the sewage in the vicinity of isolation hospitals; Brown *et al.* (1945) obtained it in the stool of a boy nineteen days prior to the onset of paralytic poliomyelitis. Kessel and Moore (1945) also recovered the virus from both tonsils and stools of non-contacts during an interepidemic period The studies of Horstmann *et al* (1946), who were able to detect virus in the blood of only one of 111 patients, indicated that its presence in the bloodstream is neither a common event nor a necessary factor in the pathogenesis

of the human disease. In recent years the feeling is crystallizing that infection is usually by way of the alimentary tract, the actual passage into the tissues being through the pharyngeal mucosa, the mucosa of the intestinal tract, or both, with subsequent central spread along the axis-cylinders of nonmedullated nerves. The studies of Howe *et al.* (1944–45) at Johns Hopkins, and Faber *et al* (1944) at Stanford University, in the first of which nasopharyngeal washings from active cases were found to produce a disease when inoculated intracerebrally in monkeys, and in the second of which monkeys caused to inhale an atmosphere containing the virus suspension delivered as a fine spray came down with the disease, certainly redirected attention towards the possibility of droplet infection or contaminated dust transmission. Indeed the very thorough study by Agius *et al.* (1945), on the small adjacent island of Gozo during the severe epidemic in Malta, made it seem almost certain that however the first cases may have been initiated subsequent spread of the disease was by nasopharyngeal droplets In recent times the white mouse, the cotton rat, the muskrat and the Syrian hamster have been added to the monkey as experimental animals that may be satisfactorily used in the study of the disease.

The early symptoms of poliomyelitis are fever, nausea and vomiting, headache, sore throat and extreme irritability with coincident malaise and restlessness; it seems that diarrhea, or a running nose and cough, occur in no more than 5 per cent of cases. Reluctance to lower the chin, and also the assumption of a peculiar position in the bed, may be seen at this stage Then, in severe cases, and either with or without a remission of several hours to several days,

culty are distinguishable: the type due to involvement of the respiratory muscles, that due to involvement of the respiratory center and usually denominated "bulbar paralysis," and that resulting from inability to swallow saliva and mucus It is felt by some but not all observers that the higher the cell count in the spinal fluid, the more severe the attack, in the prodromal stage the fluid is clear but under increased pressure In their study of a recent Chicago epidemic Andelman *et al* (1946) found a consistent and prolonged rise of the spinal fluid protein level in frank as well as subclinical cases. Rosin *et al* (1944) stated, on the basis of a study of ninety-six patients, that in the individual case there is no correlation between the severity of the disease and the sedimentation rate or white blood count In seven of nine autopsied cases, Peale and Lucchesi (1943) found myocarditis of some degree in addition to toxic and degenerative changes in the cardiac muscle Poynton (1943) reported an unusual type of outbreak of poliomyelitis in which arthritis often appeared as a complication.

The older poliomyelitic concept, that which I should like to call "orthodox",

however, would have bed rest continued until all evidences of pulmonary infection have been cleared for he had seen some cases of bronchiectasis, empyema and residual ulcerative tracheobronchitis following a protracted course of atypical pneumonia.

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due to variations in the physiologic resistance of the host. Several observers have thought that there was some evidence of connection between the harvest time for perishable fruits and vegetables in various parts of the world and the incidence of infection in epidemics there, but Toomey *et al.* (1943) failed to recover the virus from fruit washings. Of course the fact must not be overlooked that such seasonal periods may merely coincide with the height of activity of some hitherto unsuspected or at least unconvicted insect vector. The simultaneous occurrence of infantile paralysis in man and of paralytic disease in poultry has been recorded by several observers, chiefly students of the disease in the Argentine. Gordon (1945) found that three of thirty-seven dog serums, collected following the 1943 epidemic in Chicago, neutralized poliomyelitis virus; neutralization was not obtained with the serums of two chickens and six pigeons from the immediate vicinity of a case of poliomyelitis Jungeblut and Dalldorf (1946) concluded that virus-harboring house mice do not function as a source of poliomyelitic infection for man in an urban environment. At least one fact is certainly established, namely, that the virus is often recoverable from the stools of patients and of healthy contacts and from the sewage in the vicinity of isolation hospitals; Brown *et al.* (1945) obtained it in the stool of a boy nineteen days prior to the onset of paralytic poliomyelitis. Kessel and Moore (1945) also recovered the virus from both tonsils and stools of non-contacts during an interepidemic period. The studies of Horstmann *et al.* (1946), who were able to detect virus in the blood of only one of 111 patients, indicated that its presence in the bloodstream is neither a common event nor a necessary factor in the pathogenesis

observation that patients with mild poliomyelitis have muscle spasm without paralysis might be taken to indicate that in them there was only internuncial and not primary anterior neuron involvement According to this hypothesis it would be only the anterior horn cell lesion that results in motor denervations with ultimate muscle atrophy. Bodian's (1946) independent study of spasm in experimental poliomyelitis caused him to conclude that lesions in the brain

same time its opponents are relaxed in order to effect the movement; therefore in poliomyelitis the explanation for the apparent paralysis of a muscle that later recovery shows not to have been paralyzed would be that it was kept in a state of flaccidity through participation in the normal reflex, *i.e*, it would be

know quite how to send an impulse down to effect contraction in it while its opponent is in a spasm that calls for its relaxation. Bennett (1943) and others have pointed out that what is here called mental alienation is by no means a new medical entity since the loss of voluntary contraction in muscle groups

seen

Kenny concept

Watkins (1943),

it is generally recognized to occur whenever there is attempted motion with partially paralyzed muscles around a joint and also when the joint is immobilized It consists simply in the substitution of accessory muscles, or even antagonist muscles, for the proper prime movers of a joint when the afflicted individual attempts to regain voluntary control; sometimes even individual muscles contract improperly in sections rather than through their full length An example of this muscle incoordination would be the attempt of a patient to breathe with his sternocleidomastoids, his pectorals and even with the platysma in the skin of the neck when there is spasm of the intercostal muscles

In the very extensive outbreak of poliomyelitis reported by Conway and Bigwood (1946), a tabulation of patients by extent of involvement during the acute stage showed that 3 5 per cent died and 17 per cent more who survived had bulbar involvement, 10 per cent were severely paralyzed, 27 per cent moderately,

not paralyzed at all

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without any residuals was borne out in Roper's (1946) analysis of the severe 1944 epidemic in the State of Virginia. One year after their attack, 65 per cent of the survivors had recovered completely and showed no evidence of having had poliomyelitis; another 14 per cent had some slight paralysis that

that the amount of residual paralysis in any case is dependent upon the amount of destruction in the central nervous system, the latter varying tremendously in different epidemics. The concept of the Kenny group does not deny the long established pathologic attack upon the cells in the anterior horns of the cord, nor would it, I imagine, concern itself with Faber and Silverberg's (1946) data, derived from a study of eight patients dying of acute poliomyelitis, which suggest that the primary lesion occurs in the peripheral ganglia; but it does hold that many of the difficulties under which the stricken patient labors are primarily symptoms engendered by muscle spasm, muscle incoordination and mental alienation

Muscle spasm: The action of the virus on the neurons may be in some instances totally destructive so that there is a resultant permanent loss of function, but according to the Kenny concept, if I understand and can interpret it correctly, the extent of the damage is often only partial and temporary and one of its effects is the production somehow of widespread muscular spasm. This muscle spasm, which is most usual in the muscles of the back and neck, the gastrocnemius muscles, pectoral muscles, muscles of respiration, quadriceps muscles and the biceps of the arms, is felt to be principally responsible for the apparent flaccid paralysis, since it is argued that the affected muscle is not actually that one which seems to be paralyzed but its opponent which is in a state of hypertonus This hypertonus will frequently cause deformity, as in the well known "foot drop" caused by spasm of the posterior calf muscles, or an elevated shoulder from spasm in the upper trapezius which may ultimately be the cause of a scoliosis, or spasm of one quadratus lumborum resulting in a unilateral lordosis with pelvic tilt and apparent leg shortening. Muscles in spasm are usually both painful and tender and it is felt that continuance of the spasm for a long period of time results in irreversible contracture due to ultimate fibrous degeneration Spasm occurs both in muscles which can and cannot be contracted voluntarily, *i.e.*, there seems to be no direct relation between spasm and motor paralysis. Of the several attempts that have been made to study this spasm on an experimental basis, that of Kabat and Knapp (1944) is of special interest. These workers found that the spasm is apparently due to an increased discharge of motor nerve impulses from the spinal cord to the affected muscles, since elimination of this excessive discharge by spinal anesthesia or by drug block at the myoneural junction was effective in relaxing the spasm in the cases in which these methods were employed. Furthermore, it was found that the pathologic involvement of the anterior horn cells is probably not the basis of muscle spasm, for (a) studies of the chronaxie of poliomyelitis muscles in spasm showed that some did but others did not give any evidence of denervation; (b) muscle spasm similar to that observed in clinical poliomyelitis was produced in dogs by temporary arrest of the circulation of the spinal cord, and subsequent postmorten examination of the spinal cords in these animals revealed only lesions of the small internuncial neurons which lie in the region between the anterior and the posterior horns; (c) since these internuncial neurons form in a sense a switchboard mechanism controlling the motor neurons, it was felt to be a reasonable hypothesis that a lesion of these internuncial neurons might produce a localized muscle spasm on the basis of release of anterior horn cells from inhibition; (d) in going over sections of the spinal cord from sixty-eight patients who had died in the acute stage of poliomyelitis it was found that in twenty-six instances the lesions were predominantly in internuncial neurons with relative sparing of anterior horn cells. The clinical

they did after paralyzed muscles were removed from plaster of Paris bandages in former times. Some of the ritual features are superfluous and perhaps harmful: for example, the giving of an enema at the start of treatment to a child who may have a paretic bowel or bladder is contraindicated; and it may be irrational to use footboards in patients who have no evidence of leg or thigh weakness, particularly as these patients often roll about the bed at will and do not use the footboards anyway. One statement that has been frequently made, namely that poor end results in the past were due to missed muscle spasm or paralysis that would have been picked up with the Kenny technic, has in some instances apparently been disproved by the observation of scoliosis within three months of the onset in cases pronounced non-paralytic and free of spasms after receiving Kenny treatment. Many orthopedists who have seen a good many cases treated by the Kenny method feel that the end results are not much different than they were in former years; they say the patients develop spasm or retain the spasm as soon as they begin to use their muscles, regardless of the contrary claims of the physico-therapists. While admitting that patients seem to be more comfortable than they were in previous years when they received treatment with casts or no treatment at all, Fischer thought that in cases showing only neck or hamstring spasm, the answer to the question whether to pack the rest of the body depends entirely upon whether or not there is muscle pain. Blount (1947) said that patients who get along fairly well with any type of treatment do a little better with the Kenny routine, *i e.*, that in them spasm is definitely of importance and it responds well to the measures suggested. But he felt that there are other cases, the kind that are hidden by Kenny proponents when anyone comes along, that do *not* improve one bit with treatment from month to month, some of these emerge with Achilles contractures and he feels sure that modification in the method improves the end result in these cases, though in any event it is none too good.

I can no more describe the Kenny treatment here than I can the older type of treatment since both require the employment of technics to be mastered only under guidance at the bedside What follows therefore is a mere outline of the two types of treatment together with a statement of some other matters that require separate attention.

Kenny Method of Treatment

At once after the diagnosis is made in the acute stage the patient is placed at rest on a bed in which a soft blanket has replaced the sheet and boards have been introduced under the mattress to give a stiff firm surface. The attempt is made to maintain an awareness of muscle function by having the patient lie

was not handicapping though it in some instances required the temporary and in a few instances permanent use of a short brace; 13 per cent required long braces and further physiotherapy but were not totally disabled; and 8 per cent were more or less totally disabled, their disability depending upon the individual ingenuity of the patient.

Relapses and second attacks of poliomyelitis are of relatively rare occurrence. Fox and Sennett (1945), reviewing the literature and their own cases, felt there is strong evidence that pregnancy increases the susceptibility to poliomyelitis. However, infection in the mother does not seem to hamper delivery nor does the fetus seem ever to become infected. Casey's (1942) study of 36 instances in which the initial case in a neighborhood followed a single short visit to or from a prior victim of the disease, established an incubation period of four to thirty-five days with an average of twelve days. Aycock and Kessel (1943) seemed of the opinion that the period of greatest infectiousness is during the first three or four days of the acute attack; Casey *et al.* (1945) found the infectious period extending from three days before to three days after the onset of the prodromal period.

Poliomyelitis is a very ancient disease; it is thought to be represented on one of the stelae of the eighteenth dynasty (1580 B.C.) in Egypt. The first modern account of the predominating infantile type was that of Michael Underwood (1784), though many feel that there was some doubt about his cases and that Heine really established the disease as a clinical entity in 1840. Duchenne, in 1855, first pointed out the relationship of the lesions in the anterior horns of the cord to the paralysis. Negroes are thought to be much less susceptible than whites. The investigations of Hudson and Lennette (1938) indicated wide distribution of the virus throughout the world. Though the report of Mumford and Mohr (1944) regarding incidence in the tropical Pacific upset the notion that the clinical disease is rarely seen in the warmer climates, Simmons *et al.* (1944) stated that a true epidemic has never been described in the Netherlands Indies.

THERAPY

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spasm. Splints, sand-bags, or casts are not employed for immobilization, but in this early stage therapy is directed chiefly toward the reduction of spasm by the use of hot applications. Woolen packs made by cutting old blankets to proper size are immersed in boiling water at the bedside, twice rung through a tight wringer, quickly applied to the involved area, and then covered with oiled silk and dry flannel that is held in place with pins or binders if necessary. All the muscle areas in spasm must be accurately covered by these packs, but the joints are left free so that the patient will not have any sense of immobilization of the limbs. Exceptions to the latter rule must of course be made when the muscle itself covers a joint, as for example the deltoid over the shoulder joint, and the joints of the hands and feet are necessarily covered because of the small area involved. The packs are usually renewed every two hours throughout twelve hours of the day, but when spasm is unusually severe or

tion among the patients so severe that in at least one hospital the danger was averted by the routine use of more or less continuous proctoclysis. Gurewitsch and O'Neill (1946), after two years of careful observation on a large number of patients, were willing tentatively to express their impression that hot baths relieve muscle soreness and tightness faster and more effectively than Kenny packs.

Since it is felt by the Kenny group that spasm may be aggravated by frequent examination or rough handling, no active or passive movements or muscle testing are allowed during the acute stage and it is felt to be obligatory that the nursing be done with extreme gentleness. Spasm is said to be relieved in a few days to a week in some cases but in others some muscles may be required to be treated with hot packs for months. All muscle spasm, not only that involving the muscles of locomotion and the prehensile and postural movements, is attacked by the application of these hot packs. For example, respiratory embarrassment due to spasm of the intercostals and pectorals or of the

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ties in emptying the bowel and bladder. Snow (1944) emphasized the point that packing of an area should not be discontinued until it was certain that the need no longer existed, since he found it very discouraging to patients to have packing resumed after its discontinuance.

eliminated muscle reeducation is begun and is con-

only the desired muscle or group of muscles while the

and no other incoordinated contractions are permitted to occur. In short, the aim is to teach the use of the right muscle at the right time without the distracting effects of other unnecessary and undesirable muscular contractions. The

patient is placed on a treatment table in the same natural position that he occupied during the period of acute spasm, he relaxes and fixes his attention solely upon the movement that is to be attempted Usual practice seems to be for the technician to grasp the part firmly and to move it twice passively through whatever range is possible without producing pain. Then the technician, having instructed the patient what is required of him by stroking the exact insertion of the muscle group to be trained and requesting him to attempt to achieve a mental consciousness of the contraction desired, assists him once through an active-passive movement of the part, and then calls upon him to perform the motion himself through concentration on the act Should the patient's attempt result in bringing into play muscles other than the one to be trained, the attempted motion is stopped at once and the interloping muscles are put out of action either by instructing the patient to do so or by finger pressure against the muscle on the part of the technician In the beginning, when any degree of visible or even palpable motion is achieved in the muscle upon which attention is being concentrated the movement is stopped so that the patient may be left with the sense of accomplishment It is felt that at any session in which the patient is not fully cooperative or whenever he manifests fatigue the attempt must cease at once If no trace of motion is achieved it is felt that the muscle may be stimulated through its tendon by placing the muscle on a slight stretch and then moving the joint backward and forward until [illegible]

[illegible]

muscle, that muscle can eventually be returned to a functional state, "loss of tendon" is according to this viewpoint indicative of complete loss of muscular tone and considered to indicate probable permanent and complete loss of function Pool treatment and the process of reeducation under water are not practiced by the Kenny group principally for the reason that movements performed under water are felt to have no counterpart in useful human movements performed on dry land and therefore place the patient at a disadvantage when he is obliged to cope with the direct forces of gravity as affecting his everyday posture However, baths of two sorts are employed during the reeducational phase, the bath often being given just preceding the reeducation exercises on the treatment table These baths, the object of which is to help the patient retain consciousness of his body structures in the campaign against [illegible]

[illegible]

warm immersion bath before the patient is removed to the treatment table. No reeducation procedures are of course carried out in the bath.

The Older Type of Treatment

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[illegible]

cord is "spotty," there is rarely complete paralysis and ultimate degeneration of the muscle groups involved The meaning of this, to those who abjure [illegible]

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applies with the help of his physiotherapist assistants comprise principally the following.

(1) By the use of such pillows, sand-bags, splints, or other mechanical devices as are necessary the various parts of the body will be placed in physiologic rest at once, alterations in the positions of the parts being made when the extent of the paralysis has become established.

(2) Local circulation is maintained and pain is combated by the application of external heat in the form of hot wet packs or hot baths, if these can be given without disturbing the patient.

(3) When pain disappears massage is begun, with possibly immersion saline baths to obtain surface hyperemia, but without movement or manipulation of the affected parts even under water.

(4) There is gradual increase in force and duration of the massage followed by the introduction of passive movements.

(5) Active movement finally begins after careful analysis of the deterrent effects which gravity, friction and atmospheric pressure are likely to have on the movement. The advantages of under-water treatment are held to be: (a) The buoyancy of the water counteracts the influence of gravity and friction so that the sense of accomplishment cheers the patient. (b) The wide range of activity also diverts and is inspiriting during the protracted treatment. (c) Knowledge of body balance gained under water is helpful to the patient in adjusting himself to walking in braces later.

(6) When the maximum amount of recovery has been accomplished by
operative surgery
tendons and

COMBATING RESPIRATORY DIFFICULTY

The *Kenny group* concedes, as expressed by Pohl and Kenny (1943), that when respiratory difficulty is due to actual paralysis of the respiratory muscles the use of the respirator would assist the patient in breathing. But they make the point very strongly that such cases of respiratory muscle paralysis occur very rarely and that in most instances the respiratory difficulty is the result of
is to be treated by hot packs as is any
opposed
but because it interferes with the application of the hot fomentations. Pohl and Kenny (1943) said very plainly "the respirator is therefore of no use in the treatment of respiratory distress due to intercostal muscle spasm." They further stated that the respirator is contraindicated in a patient whose difficulty is due to spasm of the diaphragm because such a patient is already in a condition of what they called "literally drowning in air" and his chest expansion

respirator. This is probably the most vigorously opposed of all the pronouncements that have come out of Minneapolis, and even men who are very favor-

ably inclined toward the Kenny treatment and have indeed adopted it practically *in toto* have in many instances refused to accept this dictum, for they stoutly support such a statement as that of Wesselhoeft (1943): "I have seen the respirator relieve too many patients with acute and serious temporary respiratory embarrassment of the spinal type—patients who have recovered and walked out of this hospital to lead useful lives—to subscribe for one moment to the violent prejudice against the respirator emanating from the Kenny adherents"

In the United States respirators of the Drinker and Emerson types, the popularly called "iron lung," are preferred, but in England much use has been made of the Bragg-Paul Pulsator, an air bag placed around the patient in the manner of a corset and rhythmically inflated and deflated by an electrically

[illegible]

pressure on the chest wall, is not as desirable as that of the other respirators which operate by means of rhythmically-produced periods of negative pressure

Combating Bulbar Paralysis

When the vital centers in the medulla are affected the situation is often an extremely serious one but it is by no means always hopeless since many of these patients do recover In this state there is a marked decrease in the rate of the respirations and they become shallow and irregular both in rhythm and in depth In addition, pharyngeal and laryngeal paralysis make it impossible for the patient to swallow or to cough and the mucus is inspired and causes the "wet" type of respiratory failure, the ultimate event often being the development of a fatal pneumonitis

Long before Kenny bounded upon the poliomyelitis stage it had been decided that the use of the *respirator* is contraindicated here, so upon this *one point at least both the Kenny-ites and their opponents are in perfect* accord. The reasons for this contraindication are two· first, when the respiratory center is involved the patient's breathing cannot be made to synchronize with the machine, and second, the respirator will cause the mucus to be more forcibly drawn down into the trachea, whereas, as pointed out by Wesselhoeft (1943), the patient's own intuition prompts him to avoid this by shallow breathing *Postural drainage*, which is accomplished by elevating the foot of the bed (as much as 15 to 20°) with the patient's head turned to

[illegible]

found to render the mucus more tenacious, more annoying to the patient and more difficult to remove. In a case of laryngeal obstruction, Nelson-Jones and Williams (1945) successfully resorted to tracheotomy.

[illegible]

with openings on the side at the terminal end, comes in sizes 16, 14 and 10 French It is about 45 inches long and is preferably passed through the nose For use in such feeding, Miller (1939) mixed, ground and sieved the followin

ingredients, stored the mixture in six portions in the refrigerator and fed one portion every three hours during the day and every four hours during the night to a patient thirteen years old: 20 per cent cream, 100 cc.; milk, 1000 cc.; eggs, 6, 5 per cent vegetable, 180 gm.; 10 per cent vegetable, 100 gm.; cornstarch, 30 gm.; orange juice, 150 cc ; Karo, 96 gm.; a small amount of salt. This diet supplied something over 1800 calories per day and was satisfactory from the standpoint of mineral and vitamin content. In one case of pharyngeal spasm in which it was thought likely that the inability to pass the tube was due to spasm of the cardiac end of the esophagus, Hilbish (1945) was obliged to resort to gastrostomy, the results were considered satisfactory.

MISCELLANEOUS MEASURES

In the extensive outbreak reported by Conway and Bigwood (1946), *penicillin*, the *sulfonamides* and *gamma globulin* were all tried unsuccessfully *Convalescent* and *adult serums* have had a long trial but have failed to make a place for themselves. However, with regard to penicillin, Fox has told me that he felt it was of value when used by him during the epidemic in Milwaukee in 1944 in relatively small doses three times daily for the prevention of pneumonitis in cases of bulbar paralysis; this latter observer also feels that these patients should be treated as for *shock* (see Index) Neal (1941), whose experience in poliomyelitis has been vast, said that she had often found *spinal drainage* to be of value if there are signs of meningeal irritation, but she warned, of course, against its employment in cases of severe bulbar paralysis and in completely asthenic patients. In cases of edema of the brain, concentrated dextrose or sucrose solutions (see Index) may also be tried.

In a series of twenty cases Kabat and Knapp (1943) employed *prostigmine* as adjunctive therapy in the Kenny type of treatment, the drug appearing to accelerate recovery in most of the cases through promoting a relaxation of muscle spasm and reducing incoordination, actions which these observers felt were apparently dependent upon alteration of function of synapses in the spinal cord, *i.e* , the postulation of an entirely new kind of action for this drug. However, it is much more likely, as pointed out by Orth (1945), that whatever beneficial effect prostigmine may have is the result of its classical action in improving circulation in the skeletal muscles and perhaps the central nervous system neurons through the blocking of cholinesterase activity. Fox and Spankus (1945), in treating twenty-four acute cases, found that the drug caused only partial and irregular relaxation of spastic muscles; nevertheless they observed that in most cases its use in combination with hot fomentations resulted in perceptible and persistent relaxation. Brainerd *et al.* (1945) observed significant muscle relaxation within one hour of the hypodermic injection of prostigmine in 85 per cent of their twenty-eight early cases, control measurements having been made immediately before injection; they felt, however, that their study of continued medication with the drug merely indicated the desirability of its further extensive trial. Frankel and Funsten (1946), in treating fifty-eight subacute cases, found that the results were fairly constant and that in a fairly large percentage of the cases dramatic changes were produced. In summary, then, it would seem that further employment of prostigmine is justified until its value can be fully ascertained—which I am afraid is damning with faint praise Prostigmine is given subcutaneously in the form of the methylsulfate and orally in the form of the bromide salt, the unpleasant para-

sympathetic symptoms induced being opposed by the concomitant employment of atropine sulfate. Dosage is as follows for adults, 1/40 to 1/30 grain (1 5–2 mg) of prostigmine methylsulfate together with 1/100 grain (0.6 mg.) of atropine sulfate; for children of eight to thirteen years, 1/60 grain (1 mg) of prostigmine with or without 1/200 grain (0 3 mg) of atropine; for children of two to six years, 1/120 of a grain (0.5 mg) of prostigmine without atropine. Kabat and Knapp began oral administration in most cases after initial injection of prostigmine but in some cases oral doses alone were used. For adults [illegible]

[illegible] of prostigmine bromide and 1/200 grain (0 3 mg) of atropine sulfate three times a day. Younger children were given ¼ grain (15 mg.) of prostigmine bromide two to five times a day without atropine It was said that these doses usually did not cause toxic or unpleasant symptoms but that the balance of prostigmine and atropine had to be adjusted carefully to the individual patient to avoid such symptoms

Considerable interest was aroused by Ransohoff's (1945) preliminary report of the employment of *curare* in four consecutive cases of acute poliomyelitis, 0 9 mg. per kg. of curare in the form of intocostrin being given for the relief of spasticity with results that seemed to be excellent in this small series. How- [illegible]

PROPHYLAXIS

Hygienic Precautions.—In Chicago during a non-epidemic year, Casey (1945) made a thorough study of the relationship of cases to potentially infecting contacts. Among sixty-six persons in contact with poliomyelitis cases during the infectious period, thirty-seven developed illnesses compatible with poliomyelitis within six to fifteen days and twenty-four were definitely diag- [illegible]

as the household in which a paralytic case occurred was approached. And then there is the recognized high incidence of multiple familial cases—this incidence was 9.29 per cent in 721 cases in the series of Swartout and Frank (1944). Thus it would seem that, since in most instances poliomyelitis is almost certainly a contact disease, the more children can be isolated from each other during the summer the less likely they are to contact the malady. Unfortunately, however, the matter is not quite so simple as that because the data of Pearson and Rendtorff, cited above, did not reveal whether the *patient* is the chief distributor of virus in the creation of a focus, though these data did make it not unreasonable to assume that, in view of the high proportion of infected adults found among the familiar associates and their wider ranges of activity beyond the immediate environment, the adult carrier may represent the chief method of dissemination. Therefore, beyond the quarantining of the stricken individual for two weeks, which seems only sensible, how far are we to go? Well, if the virus radiates from the individual case and is probably more effectively dis-

absurd because it obviously could not be enforced, and even if it were enforceable it would almost certainly not effect a reduction in the incidence of the disease for the reason that subclinical or "abortive" cases, that are very likely fully as good disseminators of the virus as active cases, always vastly outnumber the recognized cases. This matter was thoroughly studied by McFarlan

of a much larger and more infectious wave among healthy persons, abortive cases and paralytic cases already in the incubation period Here in Milwaukee it has been estimated that over a long period of years at least 344 individuals are infected per recognized and reported case. In view of such an epidemiologic situation we are helpless and mass quarantine becomes, it seems to me, rather puerile. It has not yet been demonstrated that the closing of schools, theaters, bathing beaches and other gathering places, the confining of children to their homes, and the prevention of the interstate migrations of children, has in any way altered the course of an epidemic. It is interesting, as pointed out by Ward and Melnick (1944), that in the fall when schools open and chances for contact infection become greater among children epidemics of infantile paralysis fade away. In an explosive outbreak involving eighteen cases with possibly at least 100 milder infections, occurring in an extremely unsanitary Naval installation during War II, Goldstein *et al* (1946) believed that the data accumulated during the investigation pointed to food, probably milk contaminated by flies, as a common source of infection The presumptive role of flies in transmission has been supported by Ward *et al.* (1945) to the extent at least that they found the virus in food exposed to flies at infected homes within an epidemic area. However, Jungeblut and Dalldorf's (1946) study of the distribution of cases of poliomyelitis in New York City during an interepidemic phase furnished no clear-cut evidence of the existence of persistent foci or other local factors, characteristic of environment, that might favor spread of the disease Numerous studies have shown the presence of antibodies against the virus in the blood of adults in 75 to 95 per cent of instances, but the statistical study of Armstrong and Davis (1945) gave no indication that

the occurrence of paralytic poliomyelitis in children bears any relationship to the presence of antibodies in the parental blood.

Since a history of over-exertion is said often to precede an attack, many men feel it advisable to attempt to curtail children's physical activities during an epidemic In the studies of Levinson *et al* (1945) it was found that monkeys subject to exhausting exercise as well as to chilling during the incubation period of the experimental disease developed a higher incidence and more severe paralysis than did the controls.

Tonsillectomy.—It is the consensus among leading students of poliomyelitis that tonsillectomy predisposes to the severe bulbar form of the disease. Recent evidence is that of Anderson (1945), who found that in the Utah epidemic of 1943 the incidence of poliomyelitis in recently tonsillectomized children was 2 6 times that in the general child population and that 43 per cent of the bulbar and bulbospinal cases had been preceded by a tonsillectomy within thirty days of the onset. Aycock (1944), who has been a leading student of this phase of the subject, has stated that since tonsillectomy is practically always elective as to time, changing the season when it is done so as not to coincide with the season of poliomyelitis prevalence is the one preventive measure that can be used with assurance in this disease.

PSITTACOSIS

(Ornithosis)

This is an acute infectious disease of birds, easily transmitted to man The birds in which the disease is so far known definitely to occur are the following parrots, parrakeets, budgerigars, finches, canaries, pigeons, chickens and at least one member of the petrel family The disease, which is caused by a virus that is oftentimes harbored by apparently healthy birds, can be experimentally transmitted to some of the smaller rodents and to monkeys as well as to birds The virus has been cultivated *in vitro*

In man, psittacosis occurs usually in house epidemics among persons [illegible]

ported in the United States during the period 1931–1942. Cases have been traced to infected birds in shipments from many countries; I believe that in the United States many of the cases have been traceable to birds from California, simply because the raising of pet birds has become a large industry in that state.

Children are notably less susceptible to psittacosis than adults. Dunnahoo and Hampton (1945) listed figures indicating that mortality from the disease in the United States in the period from 1929 to 1942 was about 21 per cent; however, they stated that there doubtless occurred during that period many undiagnosed or incorrectly diagnosed cases. There is one recorded instance

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of a person having a second attack of psittacosis. Though the incubation period is not as yet definitely established, it is believed to be between seven and fourteen days in most instances The Meyer-Eddie modification of the serum complement-fixation test of Bedson is considered to be of great assistance in making the diagnosis.

In man the first sign is usually a chill with subsequent rise of temperature and a pulse rate that is not commensurate with the fever, also headache, backache, loss of appetite, white-coated tongue with red edges, abdominal *distention*; there may be vomiting and either diarrhea or constipation, sometimes, but not invariably, there is leukopenia. Upon this typhoid-like picture is engrafted a pneumonia in which there are pronounced physical signs of pulmonary involvement often without much sputum or pain in the chest, though the cough may be severe. Albuminuria as well as nervous symptoms are often in evidence The attack may run a course of many weeks, the pulmonary symptoms frequently continuing long after the temperature has subsided. Smadel (1943), and Favour (1943) and others, have pointed out that psittacosis is really the correct diagnosis in some cases of atypical pneumonia, but unquestionably this virus is not the etiologic agent very often in this latter disease.

THERAPY

Favour (1943), Appelbaum and Ackerman (1942), and Toomey and Lohrey (1946) all found sulfonamides of no value in their cases Turgasen (1944), Flippin *et al* (1945), and Rosebury *et al.* (1947) have each reported a case in which penicillin seemed to be of definite therapeutic value. Koch (1940), in Germany, was quite enthusiastic about his results with *trypaflavine* (acriflavine) in seven cases, using 10 cc of a 2 per cent solution intravenously daily for three or four days

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RABIES

(*Hydrophobia*)

Rat [illegible] though
many
with t
nervous system of infected animals. Webster and Clow first convincingly reported the cultivation of the virus in 1936, though apparently Kamazawa [illegible] animal
[illegible] uals,
[illegible] seems
whether among the lower [illegible]
possible for apparently healthy animals to harbor the virus as carriers. Once the symptoms of the disease appear, however, a fatal termination after terrible suffering is certain in both animals and man In the island of Trinidad, in 1931, it was proved that the vampire bat is capable of transmitting the virus between infected cattle and man, upon both of which this loathsome fellow feeds; it appears that a belt of this bat-transmitted rabies extends down through eastern South America as far as Montevideo.

There is little mention of rabies between the classical description of Aetius, a physician at the Byzantine Court in the sixth century A D., and the keener observers of the eighteenth century, such as Boerhaave and his famous

"Dumb rabies is less frequent in man than in lower animals. Its recognition is particularly necessary, so that it may be differentiated from the paralysis which very rarely occurs during or just after the Pasteur treatment. The onset may be convulsive, but the lower extremities feel very heavy and numb; then there quickly develops a condition of ataxia and progressive paralysis. Death occurs in from two to eight days from heart paralysis."

THERAPY

Treatment of the Dog.—A dog manifesting undoubted symptoms of rabies should be killed at once and his head shipped, either packed in ice or in equal parts of glycerin and water, to the nearest laboratory equipped to make a confirmatory search for the Negri bodies either directly or after injection into mice by the technic of Webster and Dawson. Veeraraghavan (1945) developed a technic for the cultivation of the protozoal parasite that he finds accompanying rabies virus in the central nervous system and has said that this cultivation technic offers both a rapid and delicate method for the diagnosis of rabies in animals. All animals definitely known to have been bitten by the rabid dog should be destroyed if possible, otherwise quarantined in isolation for three months (there has been reported, J.A M A., 115, 1109, 1940, a presumable incubation period of 113 days in a dog bitten by a rabid dog.) If, however, the dog is only suspected of having the disease he should not be killed but quarantined for observation, for a negative laboratory examination at this time would only leave the diagnosis in doubt. There need be no fear that he will recover from a "light" case during the period of quarantine, for all animals having rabies *die*. An animal showing no symptoms after three weeks in quarantine is considered not to have the disease; indeed, it is the policy of some public health departments to quarantine suspected animals only for seven to ten days since the saliva of a rabid animal does not become infectious until two to eight days before clinical symptoms appear.

Local Treatment of the Bitten Human.—Until relatively recently there has been little doubt of the paramount importance of thorough cauterization of the wound with fuming nitric acid as soon as possible after the bite has been received. But then there appeared an answer to a query in the Journal of the American Medical Association (112, 1283, April 1, 1939) to the effect that cleansing with soap and water and subsequent irrigation with saline solution might be the preferable treatment Since the point is one of quite immense importance a controversial exchange of opinion subsequently appeared in the Journal, in which it seemed to me the proponents of cauteri- [illegible] the points made by Kellogg [illegible] Health, which may be tersely [illegible] virus is not the lymphatics or blood stream, therefore the citing of evidence that particulate matter is carried away rapidly through the lymphatics from the site of its introduction has no validity here; (b) rabies virus travels centrally by way of the nerve trunks only, and very slowly, (c) fuming nitric acid not only destroys tissues and virus on the surface but it also effects some penetration and destruction at an appreciable depth; (d) since vaccination treatment can protect against only a limited amount of virus it is important that as much be destroyed at the site of entry as possible, (e) considerations of scarring should have no weight, for it is just on the face, from which the virus can most rapidly reach

the central nervous system, that the use of nitric acid cauterization is most imperatively necessary. However, one should not overlook the experimental study of Shaughnessy and Zichis (1943), who found that in the treatment of guinea-pig wounds that had been inoculated with fixed rabies virus, irrigation with 20 per cent solution of soft soap was just as effective as chemical cauterization with fuming nitric acid, possibly indeed slightly mo[re] effective.

Vaccine Treatment of the Bitten Human.—The incubation period of the disease in man is between twelve and one hundred days, with an average of forty to sixty. Hajare (1933), to be sure, recorded a case developing after fourteen months, and Iyengar (1935) after nearly three and one-third years, the possibility of fresh infection during the interval having been excluded in the opinion of both authors, but since such a student of the disease as Webster (1937), of the Rockefeller Institute, has said that one may unquestionably contract rabies merely by intimate contact with a rabid dog without actually being bitten, and since in the first stage of "furious" rabies a dog may become excessively affectionate instead of vicious, there would seem some reason to doubt the validity of these cases (incidentally, Schlotthauer, 1938, said, upon what authority I do not know, that whereas fluid saliva may remain infective for more than twenty-four hours, dried saliva is noninfective after fourteen hours) It is during the incubation period that the proper use of prophylactic vaccine will prevent the disease in the vast majority of cases; indeed, the failures constitute only 0 26 per cent in arm-bitten cases and 1.59 per cent in head-bitten cases, according to the latest League of Nations Health Section report (McKendrick, 1940) I am aware that there is currently some skepticism regarding the true significance of these figures since the variable factors are necessarily very many Was the dog rabid, did he really bite the individual, did he bite through clothing, was a potent vaccine used, was the individual one of the 75 per cent who would not have developed the disease even without vaccine?, and so forth But until there are forthcoming more significant data to be used against the vaccine than those of Denison and Dowling (1939), whose studies in Alabama brought the question to the forefront in the United States, I feel it the bounden duty of the physician to vaccinate his patient in all instances in which it has traditionally been believed such practice is indicated. Since McKendrick's (1940) analysis showed that treatment begun as late as fourteen days after exposure appears to give as good results as that begun earlier, one may safely wait for the appearance or nonappearance of symptoms in a quarantined dog before starting the treatment unless the bite has been received on the face or hands, in which case, owing to the short incubation period following wounds at either of these sites, the physician is usually well advised to begin treatment at once—unless, of course, he is firmly convinced of the dog's innocence Pregnant and nursing women may be treated with safety.

It is no longer necessary to send a patient at great expense to a "Pasteur institute" for treatment, as any physician can administer the vaccine in the improved form in which it now appears on the market. The question of "live" or attenuated vaccine, as employed in the Pasteur method and several of its subsequent modifications, versus "dead" vaccine, as employed in the Semple phenol-killed method, was to be settled at an International Rabies Conference to have been held just at the time of the outbreak of War II. However, I think the question is being settled without the Conference, for the weight of evidence

is in favor of Semple (phenol-killed), or a modified Semple (chloroform-killed), vaccine upon two *counts*: (*a*) *it is just* as effective as Pasteur (attenuated) vaccines, and (b) it is much less likely to cause postvaccinal symptoms There are numerous evidences, however, that commercial vaccines vary greatly in potency, and it is therefore fortunate that Webster (1941) devised a mouse-immunization test by which standardization can now be accomplished. Most

whom the virus has not far to travel from any point at which it is introduced

The duration of immunity in man after vaccine treatment is probably no more than fourteen months, though to be sure there are very few available data on the subject. A person bitten a year or more after taking the Pasteur treatment should again go through a full course of injections. Remlinger and Bailly (1931) reported an instance of 4 full antirabies treatments in four years; a second case of 3 treatments in four years; and a third of 2 treatments in seventeen years There were no anaphylactic accidents in any of the cases. Kohn-Richards (1939) kindly informed me that three individuals in his laboratory, having completed the Semple vaccine injections in August, found it necessary to repeat the course in the succeeding February because of a new exposure. Skin tests with the vaccine diluted 1:200 were first performed, but

first given as a trial dose and the injection was completed after two minutes, there were no untoward reactions.

I do not believe that the vaccine *per se* is actually responsible for many of the varied symptoms manifested by patients while taking the Pasteur treatment. In my own case, despite the fact that treatment was begun early and that the vaccine was for the most part self-administered, I was the victim of a certain unwonted apprehension, and was thoroughly weary of the irksome

subcutaneously in the abdomen.

Postvaccinal Accidents—Two serious occurrences, however, do sometimes accompany or follow the treatment; they are paralysis and polyneuritis McKendrick's (1940) review listed 181 paralytic accidents (48 fatalities) in a series of 1,060,832 treatments, this is one such occurrence for each 5861 persons treated and one death for each 22,100 treated. However, since these figures include accidents following the use of active as well as inactivated virus, and since inactivated virus is almost exclusively used nowadays, they do not truly present the picture—indeed, McKendrick found an incidence of paralytic accidents of only one in 8887 persons treated with phenol-inactivated vaccine. Such an incidence is certainly not high enough to be considered a contraindication to employment of the vaccine.

Treatment of Rabies in the Human.—This can only be directed toward relief of the suffering, as no cure of a proved case has ever been accomplished so far as I know. Five per cent cocaine solution may give relief if sprayed well down into the pharynx. Indicative of the degree of excitement is the experience of Hart and Evans (1939), whose patient was unable to sleep or rest and had to be shackled to the bed despite the administration of the following medication within a twenty-four hour period: 12 grains (0 75 gm) pentobarbital sodium, rectally; 10 grains (0.6 gm) phenobarbital sodium, intramuscularly; 60 grains (4 gm.) chloral hydrate, rectally, 1 grain (60 mg.) morphine sulfate, intramuscularly

Protective Vaccination of Dogs.—In a sufficiently large-scale experiment so that the findings could be accepted as having significance, Johnson and Leach (1942) found that a single subcutaneous injection of 5 cc of chloroform-treated vaccine had very considerable value in the prevention of rabies in dogs. So far as is known, Negri bodies do not develop in dogs vaccinated protectively against the disease There are no reliable figures available on the duration of protection, in Johnson and Leach's study the infecting virus was introduced thirty-one days after vaccination Casals (1945) said that while the experimental test as applied in his laboratory at the Rockefeller Institute was probably more severe than the natural infection, nevertheless he felt that 5 cc of vaccine per dog might not be sufficient to protect against heavy infection and that therefore it might be advisable to give a second dose of 5 cc in order to establish a more solid immunity It has been reported (J.A M.A., 133, 116, 1947) that in order to stop the spread of rabies through the city of New York all owners of dogs are hereafter to be required to present proof of vaccination in order to get a dog license, evidently it is the intention to accept certification of one animal injection as satisfactory Molina (1938) stated that in a region in Brazil infested with vampire bats the cattle are given one injection annually for three years and appear to acquire a solid immunity

RAT-BITE FEVER

(Sodoku and Haverhill Fever)

Sodoku is an infectious disease that follows usually the bite of a wild rat; other animals known to act occasionally as vectors are the cat, pig, dog, monkey, squirrel, ferret, weasel and field mouse. It has long been known, and principally studied, in Japan, but authentic cases are being increasingly reported from various other parts of the world. Futaki and Ishiwara discovered the causative spirochete, *Spirillum minus*, in 1915 After an incubation period of one to four weeks, the wound site becomes secondarily inflamed and soon ulcerates, there is accompanying regional adenitis, and the patient experiences a paroxysm characterized by gastro-intestinal symptoms, fever and an exanthematous rash. The symptoms last about two days and disappear by crisis, reappearing in a few days, however, and continuing a relapsing course for several months Sodoku is characterized by progressive anemia. The appearance of the organism in the blood of an albino mouse inoculated intraperitoneally with venous blood of the patient affords laboratory confirmation of the clinical diagnosis, but unfortunately *S. minus* or a morphologically similar organism sometimes occurs naturally in laboratory mice. The Kahn test is

apparently usually positive but the Wassermann reaction shows considerable variation. Mortality is about 10 per cent in untreated cases. Hitzig and Liebesman (1944) reported an amazing case of subacute endocarditis which seemed to be certainly due to *S. minus* though the clinical course and the changes observed at autopsy were similar to those observed in cases of subacute bacterial endocarditis due to *Streptococcus viridans*.

In Haverhill, Massachusetts, in 1926, there was a small localized epidemic of cases which very closely resembled sodoku save for the fact that none of the patients had been bitten by any animal prior to the onset of the illness. A few cases had previously been reported abroad. It now appears that this entity is caused by *Streptobacillus moniliformis* (*Haverhillia multiformis*), an actinomycete for which the proper name, according to Jordan and Burrows (1945), is *Actinomyces muris-ratti*. Strangeways (1933) showed that both laboratory and wild rats can act as carriers of this organism; in 1940, Allbritten *et al.* reported the first case contracted through the bite of an albino rat in the laboratory. However, it is thought that in the Haverhill outbreak the organism probably entered the blood stream through the gastro-intestinal tract.

Richter (1945) reported that of the ninety-three persons known to have been bitten by rats within an area of less than two square miles in Baltimore in the four-year period from 1939 to 1943, 10.7 per cent developed rat-bite fever. In a very exhaustive study of the entire subject of the rat-bite fevers, Brown and Nunemaker (1942) stated the feeling that probably following the bite of a rat the infection is more often due to *S. moniliformis* than to *S. minus*, but Watkins (1946) said that of the 184 cases of rat-bite fever that had been reported in the United States up to the time of his writing, thirty-

Spirillum minus	*Streptobacillus moniliformis*
History of rat-bite (or other animal bite)	May or may not have history of rat-bite
Long incubation period, from one to four weeks	*Short* incubation period significant, it may be long
Recurrence of local lesion with each onset of fever	Local lesion at onset of disease
Marked local lymphangitis and lymphadenitis	Mild adenopathy or none
Bluish red maculopapular rash occurs in some cases	Erythematous maculopapular rash occurs in most cases
Myalgia; no arthritis	Arthritis usually present
Serologic tests for syphilis frequently positive, particularly flocculation test (Kahn)	Serologic tests for syphilis rarely positive
Good response to arsenicals	No established specific treatment
Animal inoculation Spirilla in blood stream	Animal inoculation frequently arthritis and death; *S. moniliformis* in heart's blood and local lesions
Agglutination tests not of definite value	Agglutination tests usually positive
Blood culture negative	Blood culture positive

In the fatal case of rat-bite fever due to *S. moniliformis* reported by Blake *et al.* (1944) the principal visceral lesion at autopsy was focal myocarditis.

THERAPY

... agents in the treat-
... *formis* cases in which
... esponse was prompt

a similar case at five days. But since, in the eleven proved cases of Taft and Pike (1945) at an Army hospital in Texas, all gave a history of sleeping on the ground in a tick-infested area on the sixth or seventh day prior to the beginning of their illness, it seems to me that infection by a stray tick would have to be excluded before accepting these infantile cases as arising congenitally. Occasionally sporadic cases are seen in states outside the West and Southwest and a few have been recorded in Canada.

The causative organism of the European variety of relapsing fever, *Borrelia recurrentis*, was discovered by Obermeier in 1873; that of the African variety, *B. duttonii*, independently in 1904 by Ross, Nabarro and Milne in Uganda, and Dutton and Todd in the Congo The causative organism in the American cases, *B. novyi*, is similar to *B. recurrentis* morphologically but dissimilar serologically. Dutton succumbed to African relapsing fever in proving its transmission by a tick. It is almost certainly established that small rodents act as the reservoir for these organisms and that certain spirochetal infections in opossums, porcupines, armadillos, monkeys, jackals, calves and horses are identical with relapsing fever in man.

The symptomatology of relapsing fever varies somewhat with localities but there is usually a very sudden onset with chilliness, severe headache and pains all over the body, dizziness, gastro-intestinal symptoms and a high fever. The spleen is almost invariably enlarged, the liver much less often, jaundice is not infrequent, especially at the crisis In a variable proportion of cases there is an erythematous or petechial rash, usually starting on the neck D'Ignazio and Codeleoncini (1946) reported eighteen cases with symptoms resembling those of ordinary pneumococcal lobar pneumonia and diagnosed as relapsing fever only when enlargement of the liver or spleen, and failure of response to sulfonamide drugs, led to a further laboratory examination and the finding of the *Borrelia.* It seems to me, however, not to be unduly severe to wish for independent confirmation of such findings before accepting them. After a variable number of days the symptoms disappear by crisis with a drenching sweat, following which the patient seems [illegible] week; then comes a relapse that is [illegible] ack. Wolff (1946), in an analysis [illegible] condition during War II, *found that the initial attack lasted from five to fifteen days* whereas subsequent attacks were of much shorter duration, rarely lasting longer than five days. In Chung and Chang's (1939) very useful statistical study *of 337 cases in* North China, there was an average of three to five *relapses in* untreated cases, a higher number than is usually expected, I believe, though in rare instances twice this many have been reported.

Relapsing fever offers many pitfalls in differential diagnosis, particularly in the tropics where many other possibilities confuse the picture. According to Scott (1944), the central nervous system was invaded in a relatively high proportion of cases contracted in the *Libyan Desert* during War II. It is easier to detect the organism in the blood of an inoculated small laboratory *animal than in that of the patient;* possibly Stein's (1944) new antigen may prove useful in the development of a serological diagnostic test The death rate has been quite high in some outbreaks, but Manson-Bahr (1946) said it is usually below 6 per cent, it was *3.5 per cent* in the 340 cases studied by Robinson (1942) in Abyssinia. Many complications may occur during convalescence

and cause infarction in the various organs; premature contractions, paroxysmal tachycardia and heart failure may occur; and of course the occurrence of subacute bacterial endocarditis is the most dreaded complication of all. Calcareous aortic stenosis is presumably of rheumatic origin.

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Rheumatic fever occurs most frequently in children of school age and is disposed to return many times, but a first attack may appear at any period from infancy to old age In Cohn and Lingg's (1943) exhaustive study of more than 3000 cases the disease was found to begin more often at about eight years than at any other age; at fifteen, which was the mean age at onset, 70 per cent of persons afflicted had already acquired the disease. These workers found that in youth the onset of the disease is characterized by polyarthritis in about half and by carditis or chorea in about one third of the cases, whereas in adult life the onset is characterized chiefly by polyarthritis and, with advancing age, by the appearance of valvular lesions alone. Rheumatic fever is encountered with greatest frequency during the late winter and the spring months in the United States, in fall and early winter in England, with various seasonal distributions on the Continent. It is relatively infrequently seen indigenously in the southern United States and until recently had been considered to be almost unknown in the tropics and subtropics, numerous recent observations have dispelled the latter idea though at the same time showing that its presence in the warm lands is of a rather "spotty" nature Hardgrove *et al* (1946) found that the course of the disease and the resultant cardiac damage on the Isthmus of Panama resemble these manifestations as seen in the United States There is a considerable body of evidence that the tendency to contract rheumatic fever is inherited; indeed Wilson (1947) is willing to say that if both parents have rheumatic disease all their progeny will probably have rheumatic disease. At least one authentic case of intrauterine rheumatic heart disease has been recorded. The evidence that rheumatic fever is a "house disease" is not convincing.

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are afflicted with rheumatic heart disease, which thus incapacitates about 1 per cent of our wage earning population. As far as hospital admissions are concerned, Paul (1947) reported that a ten year study at the New Haven Hospital showed cases of rheumatic fever, both active and inactive, constituting the third largest number of admissions for infectious diseases; tuberculosis headed the list, syphilis stood second, and rheumatic fever

RHEUMATIC AFFECTIONS

Rheumatic Fever

Rheumatic fever in its acute phase is characterized clinically by fever, pronounced toxemia, proliferative and exudative arthritis, usually proliferative valvulitis (endocarditis), and sometimes pericarditis, pleuritis, and a type of intercurrent pneumonitis in which the onset is without chill and often without cough. The characteristic pathological entity, consisting of a minute, focal, proliferative lesion known as the Aschoff body, is seen most typically in the myocardium, but this lesion does occur elsewhere in the body since in its generalized involvement of the fibrous tissues in the vascular bed the rheumatic infection involves not only the heart and joints but also the lungs, pleura, kidneys and numerous other tissues, though with the exception of Sydenham's chorea early clinical disturbance of the central nervous system seems rarely to occur.

Following acute naso-pharyngitis or tonsillitis, or scarlet fever or chorea, or symptoms resembling those of acute appendicitis, or without any prodromata at all, the bout of rheumatic fever often becomes suddenly established with high fever, sweating, prostration, and very painful and tender polyarthritis Sometimes there occur erythematous or ecchymotic skin manifestations, and in children non-painful and non-tender groups of subcutaneous rheumatic nodules often appear along the tendons of the backs of the hands, elbows and knees and in the spinal and occipital regions. But sometimes rheumatic fever begins very insidiously and in these cases the diagnosis will cause considerable difficulty Furthermore, rheumatic heart disease occurs without having been preceded by clinically recognizable rheumatic fever; Cohn and Lingg (1943) found that before the age of ten valvular lesions alone are the first manifestation in only about 15 per cent of cases, after the age of forty in almost 80 per cent. It is now considered that suspect should be the child who loses appetite and weight unaccountably, becomes pale and complains of muscle pain—but "growing pains," which occur principally in the lower extremities and at night, should not be confused with the joint pains of subclinical rheumatic fever. In the frank form, the successive involvement of two or three sets of joints may be completely recovered from in ten days to two weeks, but more often several sets of joints are simultaneously involved and the attack lasts much longer. Experience shows that recognizable heart involvement occurs in about 70 per cent of cases and many investigators believe that there is some degree of damage in the remaining cases even though it may not be demonstrable at the time. The experience of Boone and Levine (1938), according with that of many others, was that the incidence of cardiac damage of recognizable degree is much greater if there is also a history of chorea The signs of cardiac involvement—development of murmurs, pericardial rub, elevated pulse rate during sleep, conduction changes observable in the electrocardiogram, beginning congestive failure—should be diligently sought, not because there is much that can be done to forestall or limit the involvement during the acute attack, but for the important reason that accurate knowledge of the time of its appearance and the extent of its existence will dictate the management of the convalescence. The cardiac manifestations of rheumatic fever may take many forms: the patient with aortic stenosis is subject to fainting spells; in the individual with mitral stenosis there may occur episodes of pulmonary hemorrhage and, if there is an associated auricular fibrillation, mural thrombi may detach

and cause infarction in the various organs; premature contractions, paroxysmal tachycardia and heart failure may occur; and of course the occurrence of subacute bacterial endocarditis is the most dreaded complication of all. Calcareous aortic stenosis is presumably of rheumatic origin.

The exact place of such laboratory diagnostic aids as the sedimentation index, the Weltman reaction, the formol-gel and the anti-fibrinolysin and anti-streptolysin has not been determined, I believe. Woods and Comroe (1945) found the Mester (salicylic acid) test wholly unreliable as a diagnostic aid. Rosenberg (1947) feels that electrocardiographic changes, particularly prolongation of the P-R interval, are strong evidence in support of a diagnosis of rheumatic fever provided that other infections producing similar changes, such as pneumonia, diphtheria, mumps and German measles are excluded. Taussig and Hecht (1938) recorded the beginning of hypertension a number of times during acute rheumatic episodes. The intensive study of Bruetsch (1944) emphasized the occurrence of late cerebral sequelae of rheumatic fever.

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Rheumatic fever is many times more prevalent among the poorer classes than among persons better housed and fed Martin (1945) estimated that about 40,000 lives in all age-groups are taken each year in the United States by rheumatic heart disease or carditis, the average age of death being about thirty years. He further estimated that from 800,000 to 1,000,000 individuals are afflicted with rheumatic heart disease, which thus incapacitates about 1 per cent of our wage earning population. As far as hospital admissions are concerned, Paul (1947) reported that a ten year study at the New Haven Hospital showed cases of rheumatic fever, both active and inactive, constituting the third largest number of admissions for infectious diseases; tuberculosis headed the list, syphilis stood second, and rheumatic fever

third. Ryle (1946) stated that in England and Wales the annual number of deaths from rheumatic heart disease is 16,000. The importance of dampness and low altitude as predisposing factors is undecided, but in Hedley's (1941) exhaustive statistical analysis of a large number of cases in Philadelphia hospitals no such association could be established Rheumatic fever is extraordinarily rare in diabetics but shows no marked racial predilections

Hedley's (1941) statistical study of 862 cases indicated that the first attack of rheumatic fever is fatal in 3 5 to 4.5 per cent of instances, the mortality being even higher if cases of rheumatic carditis without arthritic manifestations are included Cohn and Lingg (1943) found that when the disease begins in childhood, 69 per cent survive childhood, 35 per cent survive adolescence, 18 per cent reach the age of thirty, and 5 per cent go on beyond the age of forty-five. When the disease begins in adolescence, 85 per cent survive this age period, 55 per cent reach the age of thirty, and 21 per cent the age of forty-six or more. When the onset is in the twenties, 23 per cent, and when it is after thirty, 44 per cent survive the age of forty-five.

De Baillou (1538-1616), whom Crookshank declared to be "the first epidemiologist of modern times," introduced the term "rheumatism." It was as recently as 1836 that Jean-Baptiste Bouillaud established what he called the "law of coincidence" between the occurrence of heart disease and this malady. In the epidemics of acute rheumatic fever occurring among soldiers and sailors in training camps in England and the United States during War II, there was usually an apparent association with streptococcic infections; such an association has also been observed in outbreaks in schools and institutions in civilian life The most attractive current hypothesis regarding the etiology of rheumatic fever presents the disease as an entity initiated by infection with a hemolytic streptococcus but precipitated in its exacerbations by many nonspecific factors For example, recurrences during convalescence may follow in a few hours upon active immunization with bacterial proteins or horse serum, severe sun burn, fracture of the long bones, tonsillectomy, tooth extraction or splenectomy. Coburn (1945) feels that the sensitization of the rheumatic individual is not confined to a product of the hemolytic streptococcus; this would certainly offer a simple explanation for exacerbations in a rheumatic patient who may at the time be refractory to a superimposed hemolytic streptococcus infection of the throat. Gregory and Rich (1946) have presented strong experimental evidence in support of the view that the lesions of rheumatic fever are due to hypersensitive reactions. Coburn, in an attempt to systematize the concept, recognizes three phases of rheumatic heart disease: (a) his phase one is a hemolytic streptococcus infection that is usually mild and nonsuppurative and is followed by prompt clinical recovery; (b) phase two is the period of one to three weeks after recovery from streptococcal infection during which time some streptococcus product or constituent is conjugated with human material to form an antigenic complex, (c) during phase three this complex induces the formation of secondary antibodies that react not only with the circulating secondary antigen but also with the antigenic component in endothelial tissues. This latter interaction gives rise to the biochemical changes characterizing rheumatic activity, which is usually polycyclic.

THERAPY

Salicylates.—*Efficacy.*—That the salicylates usually afford great relief in rheumatic fever is well known Indeed, I imagine it will require a much more extensive study than that of Murphy (1945), who failed to find mensurable evidence of the subsidence of articular symptoms in twelve cases, to upset the great accumulation of bedside experience attesting objective as well as subjective improvement under these drugs The fever promptly subsides and there is often a considerable and sometimes a complete reduction of the pain, heat, redness, swelling and limitation of motion in the affected joints Manchester (1946) undertook to determine whether the salicylates exert a more specific modifying effect on the course of the disease

adequate therapy and that polycyclic recrudescences in residual chronic infection occur less frequently However, the effect of the salicylates upon the total duration of the disease and upon the incidence and duration of the cardiac involvement is the subject of a controversy that blows now hot now cold through the years Manchester's study resulted from Coburn's (1943) claim that with salicylates he had protected thirty-eight young adult rheumatic patients against the development of valvular heart disease while twenty-one of sixty-three patients given what he considered inadequate dosage did develop physical signs of heart disease. Discussing Coburn's claim, Rosenberg and Hench (1946) pointed out that he spoke of protecting against the development of *valvular* heart disease and of the development of *signs* of heart disease in the unprotected group, thus leaving it not clear whether mild cardiac lesions were also prevented in the "protected" group. No electrocardiographic data were supplied in Coburn's report. Watson

salicylates in rheumatic fever is due to their interference in some way with the antigen-antibody reaction which they believe underlies the tissue inflammation. The most interesting new approach toward the understanding of salicylate action in rheumatic fever has been made by Guerra (1946), in Mexico. It has been shown that in various forms of connective tissue there is a viscid ground substance from which may be isolated the polysaccharide, hyaluronic acid. This ground substance acts as a barrier to penetration and spread of foreign matter. In rheumatic fever, in which the mesenchymal tissues are especially involved, it is felt that the rapid spread of the infecting agent and its inflammatory sequence evidence a removal of the protective connective tissue ground substance barrier; this seems all the more likely since there has been found in some bacterial and tissue cells an enzyme, hyaluronidase, that hydrolyzes and degrades hyaluronic acid, decreases its viscosity, and allows an increase in permeability and spread of foreign material through connective tissues. In Guerra's work he has shown that the administration of sodium salicylate inhibits the spreading effect of hyaluronidase; for comparison he studied sulfadiazine and found that it did not have this effect. These studies are being very closely watched because they possibly open up an entirely new field of investigation and explanation.

Choice of Compound.—In therapeutic effect there appears to be practically no difference between sodium salicylate and acetylsalicylic acid (aspirin) in equal dosage. Both cause salicylism and rather easily induce acidosis unless guarded with sodium bicarbonate. A few years ago, Coca *et al.*, and Prickman and Buchstein, stated that aspirin hypersensitivity (there have been a few fatalities) is the most frequently encountered form of drug allergy, but I think Gardner and Blanton (1940) did well to point out that the apprehension in the *profession subsequent to this statement is perhaps unwarranted* since the number of individuals reacting violently to this drug must surely be very small in proportion to those who take it—they found that the amount sold in the United States in the year of which they had record was 5,143,672 pounds In cases of cardiac failure it might be advisable to use aspirin instead of sodium salicylate in order to avoid the administration of undesirable sodium, though since much of the aspirin is absorbed from the intestine as sodium salicylate it is doubtful how effective this substitution really is. It is said of the salicylic ester of salicylic acid, salysal, that it is effective in lower dosage than either sodium salicylate or aspirin and also that it causes less gastric irritation; but less experience has been had with this than with the two older agents.

Administration by Mouth.—During War II, Coburn (1943) stated his belief that in order to accomplish maximum progressive subsidence of rheumatic inflammation one should endeavor to maintain a plasma salicylate level of 35 [illegible] mpletely ineffec- [illegible] ective level by a [illegible]

[illegible] 186 [illegible] sage young adults in both severe and moderate groups, [illegible] seemed to accomplish just as much as high dosage. The only apparent advantage of high dosage in the Warren series appeared to be its ability to reduce

temperature more rapidly. Huntington *et al* (1946) found that high dosage

with one death in children who were being given Coburn's dosage for young

second patient on the twenty-second day of oral administration, with a blood

ing toxic symptoms This total dosage is divided into six fractions administered at four-hour intervals throughout the day and night, sodium bicarbonate being given simultaneously in doses one-half that of the salicylates. The patient therefore receives from 12 to 24 grains (0 8 to 1.6 gm) of salicylate and 6 to 12 grains (0.4 to 0 8 gm.) of sodium bicarbonate every four hours Since these drugs are best tolerated after meals, Watson has the doses falling between meals preceded by crackers and a glass of milk in order to lessen epigastric burning and discomfort. When nausea, vomiting, deafness or excessively rapid respiration (tachypnea) persists, indicating the limit of systemic tolerance for salicylate, he decreases the dose or increases the amount of sodium

lates for a period of two weeks after the joint and other symptoms, the leukocytosis, the elevated sedimentation rate, the fever and the electrocardiographic abnormalities have all disappeared He then reduces dosage gradually over a week to ten days and finally discontinues the drug if the patient's condition remains unchanged.

effervescent tablets of sodium salicylate are also available. The 6 per cent alcoholic elixir of sodium salicylate contains about 40 grains (2.5 gm.) of salicylate per fluid ounce (30 cc.). Sodium salicylate may also be prescribed extemporaneously in a flavored mixture with bicarbonate, as in the following prescription:

℞	Sodium salicylate	ʒv	20.0
	Potassium bicarbonate	ʒiiss	10.0
	Aqueous elixir glycyrrhiza	℥iv	120.0
	Syrup glycyrrhiza to make	℥viii	240.0

Label One or more teaspoonfuls in water as directed. (Note: each teaspoonful contains 5 grains (0.3 gm.) salicylate and half as much bicarbonate.)

Leaving all quantities *unchanged, the above may* be *entirely* altered in flavor by making any one of the following paired substitutions for the aqueous elixir and syrup of glycyrrhiza (I am *employing vehicles usually liked* by children), though it is well to note that any of these mixtures may become discolored and develop a dark precipitate upon standing:

Cinnamon water
Syrup cinnamon

Spearmint water
Syrup glycyrrhiza

Water
Syrup cacao

Water
Syrup raspberry

Compound elixir vanilla
Syrup tolu

Supplementary Para-aminobenzoic Acid by Mouth.—In a very interesting case of typical acute rheumatic fever in a man forty-two years of age in whom it was *impossible to achieve a higher salicylate titer than* 15 mg. per cent after twenty-three days of high dosage, Dry *et al.* (1946), of the Mayo Clinic, empirically administered 60 grains (4 gm.) of para-aminobenzoic acid, followed by 30 grains (2 gm.) every two hours around the clock. The dose of salicylate remained unchanged. The result of this addition of para-aminobenzoic acid was that there occurred a steady increase in the plasma salicylate titer from 12.5 to 34.5 mg. per cent by the seventh day of therapy with para-aminobenzoic acid, after this the figure levelled off until, when the use of para-aminobenzoic acid was discontinued, it decreased fairly abruptly *to 15 mg. per cent by the eleventh day. On each occasion thereafter when* para-aminobenzoic acid was administered the same effects on the salicylate level were *noted*, and *each time* that the *salicylate* level was in this way forced up to 37.5 mg. per cent there was a dramatic and complete clinical response. All medication was discontinued twenty-six days after the initial administration of para-aminobenzoic acid and the patient was allowed to continue at bed rest. Within four days there was a recurrence of symptoms and these again responded completely to the salicylate-para-aminobenzoic [illegible] healthy men,

increases considerably upon the [illegible]
(0.155 gm.) of para-aminobenzoic acid per day. Further development of this new therapeutic approach is awaited with interest, though para-aminobenzoic acid is not itself an innocuous agent (see Rickettsial Diseases).

Intravenous Administration.—During War II, Coburn (1943) introduced the intravenous administration of sodium salicylate and claimed *superior* results with it. More recently, Manchester (1946) has said that his preferred treatment *for severely ill young adults with cardiac failure* is the daily intravenous administration, during six hours, of 150 grains (10 gm.) of sodium *salicylate in 1000 cc.* of Ringer's lactate solution; intravenous therapy is

continued for four to seven days and is followed by high-dosage oral therapy for as long as necessary, refractory cases being shifted back to intravenous infusions as indicated. However, intravenous salicylate therapy has received much sharp criticism and has gained few staunch advocates Taran and Jacobs (1945) found that it did not offer significant advantages over the oral route, with which they were easily able to achieve the desired plasma levels, and that its employment in rheumatic carditis might be hazardous. Certainly a strong talking point in favor of intravenous therapy is that with it a continuous high plasma titer of salicylate might be maintained, but actually Wegria and Smull (1945) found the titer falling below the optimum level between infusions. Warren *et al* (1946) observed no therapeutic advantage from intravenous administration and in some cases they were obliged to discontinue it because of constant vomiting, in these patients they were able to resume salicylate therapy in large oral doses after a few hours without difficulty. In Manchester's (1946) thirty-five patients treated intravenously, delirium occurred in 17 per cent of instances, it always subsided within forty-eight hours after salicylates were stopped Since no mental reactions were observed in patients while on oral therapy or in those in whom intravenous therapy was instituted after the acute phase of their illness had subsided, Manchester felt that the reaction could be attributed to the abrupt and rapid rise in blood salicylate levels associated with intravenous therapy in acutely ill patients who have not built up an antecedent tolerance to the drug In this series of patients a mild acceleration of respiration attributed to direct stimulation of the respiratory center was more frequently observed than during oral therapy, in three cases this acceleration in conjunction with already existing dyspnea of cardiac failure was sufficient to preclude temporarily the further use of salicylates by either intravenous or oral routes. Rosenberg and Hench (1946) said they felt that patients with rheumatic fever given salicylates orally were not being denied a superior more scientific form of therapy.

Rectal Administration—Wilson (1947) and many others stretching back through a long period of years have found the rectal route quite satisfactory. To individuals in whom there is vomiting from causes other than salicylate administration, Watson (1947) gives sodium salicylate 45 to 60 grains (3 to 4 gm) dissolved in 150 to 200 cc of warm starch water three to four times a day. In fact, a few years ago Conner (1942) said that in his hospital he had made rectal administration the regular routine. However, Huntington *et al.* (1946) found this method of introducing the salicylates cumbersome and inefficient.

Toxicity.—During the administration of salicylates, tinnitus and diminished hearing are of very frequent occurrence and of little practical im-

[illegible]

stage the use of intravenous saline is necessary in order to relieve the symptoms. Coombs *et al.* (1945), of this same group of observers, had earlier shown

that excessive salicylate induces hyperventilation with resultant alkalosis, water retention and diminished renal function. The administration of sodium bicarbonate checks hyperventilation through increasing the secretion of salicylates.

Caravati (1946) performed gastroscopic examinations on twenty patients suffering nausea or vomiting on salicylates, twelve of the patients receiving the drug intravenously and the other eight taking it by mouth. He concluded that the gastric symptoms are probably due solely to action on the higher cerebral centers since no discernible gastric reactions could be determined by the gastroscopic studies. He found also, by gastric aspirations, that the drug is not secreted into the stomach regardless of the height of the plasma level. Then, with Cosgrove (1946), he determined that intravenously administered salicylate produces nausea, vomiting and dizziness as frequently as does that given by mouth, and that the oral administration of sodium bicarbonate lessens nausea in both cases not by local action but through raising the *p*H of the urine, promoting salicylate excretion, and hence lowering the salicylate blood level. *Per contra*, the oral administration of ammonium chloride will reduce urinary salicylate excretion and raise the salicylate blood level.

Meyer and Howard (1943), confirming the animal experimentation of Link *et al* (1943) in which it was found that salicylic acid acts like dicumarol in [illegible]

vitamin K with the salicylate prevented these developments and felt it at least theoretically possible that the not unusual hemorrhagic manifestations of acute rheumatic fever might be due in some cases at least in part to the large doses of salicylate so commonly administered Owen and Bradford (1946), studying twenty-five patients in acute rheumatic fever in whom they maintained plasma salicylate levels of about 35 mg. per cent, found that in two cases the prothrombin level fell below 20 per cent and in twelve cases below 30 per cent of normal. Five patients developed epistaxis, one of them severely, and two of the five also showed the small splinter hemorrhages under the finger nails that are seen in patients undergoing dicumarol therapy. In all instances salicylate therapy was continued and bleeding was controlled by ordinary measures; spontaneous return of prothrombin time to normal occurred in [illegible]

treatment; no instance of bleeding was observed after the third week of [illegible] ment. In Clausen and Jager's (1946) series of twenty-four cases, in spite of the frequent occurrence of marked prolongation of the prothrombin time of patients receiving salicylates, there was evidence of bleeding in only one instance, a healthy adult patient who had bleeding from the nose and gums when there was marked hypoprothrombinemia (20 per cent of the control curve) and severe salicylate intoxication. In another case in which there was equally severe prothrombinemia and a fatal salicylate intoxication, autopsy revealed only a few insignificant hemorrhages from the serous membranes. In five other patients with severe salicylate intoxication and great reduction in prothrombin content of the plasma, no spontaneous hemorrhages were observed. Though

Clausen and Jager usually found the severity of the hypoprothrombinemia proportional to the plasma salicylate level, neither Butt *et al* (1945) nor Govan (1946) was able to observe such a correlation. Indeed, Govan found

salicylate concentration of the plasma; however, I do not know how much importance should be attached to this statement since it seems to have been

for a short period only.

Watson (1947) said that the use of a little petrolatum, or one or two drops of mineral oil in the nose twice a day, often eliminates epistaxis in those prone to develop it during rheumatic fever

Aminopyrine (Pyramidon).—This drug frequently acts more strikingly and rapidly than the salicylates, it does not cause unpleasant gastro-intestinal

of patients who are easily poisoned by the salicylates Watson (1947), of the

grains (2 to 3 gm.); he feels it especially important with this drug to administer it from early morning until late at night, *i.e.*, giving the first dose when the patient awakes in the morning and the last dose at 8 or 9 o'clock at night in-

the white blood count and ceases to use the drug when *this count falls to 4000*

comes quite into vogue in the treatment of rheumatic fever where the patient's blood picture can be closely watched.

to evaluate in the individual case the role of digitalis on the one hand and the effect of cessation or progression of the rheumatic process on the other. Gold (1947) pointed out that frequently one may see a patient with active rheumatic carditis whose cardiac failure continues to progress even while lying in bed and fully digitalized; he feels that probably the active rheumatic process may

inherent fault of digitalis but the fact that the rhythm, *being usually a sinus* tachycardia rather than auricular fibrillation, presents no satisfactory guides to

with auricular fibrillation can be controlled, that in a few instances when the

symptoms are those of both left and right-sided failure, the drug

le in the vast

lis is definitely

ncarditis with

failure.

Diuretics.—Watson (1947) says that he has found the mercurial diuretics beneficial in some cases of rheumatic heart failure, but Harris (1946) said that in his experience they have been more successfully employed than digitalis. Taran (1947) finds this diuretic therapy not infrequently a life-

since these drugs will control the advancing cardiac edema

ncy is increased.

erienced observers, is con-

oxygen atmosphere during

of reducing the work of the

age, his opinion was based

principally upon experience gained with rheumatic disease in children.

Bed Rest during and Rest after the Attack.—It is usual practice to keep the patient in bed, *without bathroom privileges*, until all rheumatic activity has ceased; Eggleston (1947) feels that, in adults as well as in children, one

should wait a bit longer, perhaps even a few weeks, before permitting resumption of physical activities Gold (1947), however, asks the very practical question whether it is more harmful to have the child jumping about in the room than jumping about in the bed Cahall (1946) has found the following postulates useful in determining the end of the active stage· (a) a persistently

sedimentation rate presents a special problem, lets these children be up and about and says that in the course of many years' experience she has had no reason for changing this practice; a thorough search in these cases sometimes discloses an enlarged lymph node, a postnasal discharge, sinusitis or some other cause for the elevated sedimentation time In a study of young adult patients during War II, Robertson *et al.* (1946) permitted such activities as sitting in or out of bed and walking to the lavatory when joint discomfort did not prohibit it, the latter occurrence being rare forty-eight hours after the patient was placed on adequate amounts of salicylates. Regulated ambulation was permitted in the presence of any cardiac phenomena unattended by congestive failure, the patients being instructed to cease their activities before the appearance of dyspnea, fatigue or other distressing symptoms. Thus in this study the patient's comfort alone was the determining factor regarding his bed status and physical activity. Robertson *et al.*
activity as a result of tl
enforced prolonged bed r
in young adults, and since it *seemed* unnecessary for the achievement of rapid recovery, they invited attention to the desirability of a reinvestigation of the

he does not restrict such a patient in any way, even permitting participation in competitive sports. This was essentially the attitude taken by the War Department during War II. "The patient who has made a satisfactory recovery from rheumatic fever can be assured once he is physically fit that limitation of physical activity is not helpful in protecting against additional attacks of subsequent heart disease and therefore is not indicated . . . even in a large proportion of individuals with residual cardiac lesions of rheumatic origin, moderate physical exercise is beneficial rather than harmful. Whether or not crippling heart disease results from rheumatic fever as a rule depends on whether repeated attacks occur "

Dietetics.—In the acute attack the patient may be fated for a long siege of pain that is exhausting to both mind and body, therefore his nutrition should be maintained at as high a point as possible. In the beginning the diet as suggested for use in pneumonia will suffice but as soon as the patient is willing to eat he should be given whatever of nutritious foods he will take without any planned avoidances or stresses upon either proteins, carbohydrates or fats. The fluid allowance advocated for pneumonia patients

should wait a bit longer, perhaps even a few weeks, before permitting re-

postulates useful in determining the end of the active stage: (a) a persistently normal temperature after salicylates or other antipyretics have been omitted; (b) a pulse rate normal for the patient's age, (c) normal blood sedimentation rate; (d) no rheumatic nodules, (e) no choreiform movements; (f) no signs of congestive failure; (g) no serous membrane involvement; (h) no intercurrent disease or infection, (i) no electrocardiographic abnormalities. Wilson (1947), recognizing that the child who is normal except for an elevated sedimentation rate presents a special problem, lets these children be up and about and says that in the course of many years' experience she has had no reason for changing this practice, a thorough search in these cases sometimes discloses an enlarged lymph node, a postnasal discharge, sinusitis or some other cause for the elevated sedimentation time. In a study of young adult patients during War II, Robertson *et al* (1946) permitted such activities as sitting in or out of bed and walking to the lavatory when joint discomfort did not prohibit it, the latter occurrence being rare forty-eight hours after the patient was placed on adequate amounts of salicylates. Regulated ambulation was permitted in the presence of any cardiac phenomena unattended by congestive failure, the patients being instructed to cease their activities before the appearance of dyspnea, fatigue or other distressing symptoms. Thus in this study the patient's comfort alone was the determining factor regarding his bed status and physical activity. Robertson *et al* were unwilling to advocate indiscriminate physical activity as a result of their findings but, since they were convinced that enforced prolonged bed rest provokes a high incidence of anxiety neurosis in young adults, and since it *seemed* unnecessary for the achievement of rapid recovery, they invited attention to the desirability of a reinvestigation of the traditional regime of protracted rest in bed.

Once the rheumatic heart disease has reached a quiescent state, Eggleston (1947) believes that if the patient can perform any vigorous act without inducing cardiac symptoms, he will not be harmed by that act. In short, he does not restrict such a patient in any way, even permitting participation in competitive sports. This was essentially the attitude taken by the War Department during War II. "The patient who has made a satisfactory recovery from rheumatic fever can be assured once he is physically fit that limitation of physical activity is not helpful in protecting against additional attacks of ...

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may even have to be increased here; the salt addition is not bad either, except in the presence of cardiac failure, for the sweating patient is losing salts as well as water.

Miscellaneous Measures.—*Sulfonamides and Penicillin.*—Not only are these drugs of no therapeutic value in rheumatic fever but their use may actually aggravate the severity of an attack.

X-Ray Therapy.—In 1937, Levy and Golden stated their belief, upon the basis of eleven years' experience in forty-eight patients, that irradiation of the heart deserves a place in the therapy of properly selected cases of active carditis; in 1946 they repeated their earlier conclusions that: (a) irradiation relieves cardiac pain in patients who do not have aortic insufficiency; (b) cases with low-grade activity and without signs of congestive failure appear to be most benefited whereas acute cases are not improved; (c) no harmful effects are noted; and (d) roentgen irradiation of the heart deserves a place as a therapeutic measure in properly selected cases of active carditis But what Levy and Golden did not state in their latest communication was whether they had enlarged their own series or knew of such a series that had been effectively handled by other observers Griffith and Halley (1946) failed to find roentgen therapy effective, but Levy and Golden felt that the discrepancy could be easily explained since Griffith and Halley seemed to be principally concerned with the general manifestations of rheumatic fever rather than primarily with its cardiac aspects.

Succinate Therapy—Gubner and Szucs (1945) used a calcium double salt of benzoic acid and succinic acid benzyl ester in the treatment of fifty-five cases of acute rheumatic fever and compared the results with sixty-five cases simultaneously treated with salicylates. They found that the succinate

significance.

Antireticular Cytotoxic Serum.—Among the numerous conditions in which the antireticular cytotoxic serum of Bogomolets is supposed to exert a favorable effect is "rheumatism." However, Bach (1945), in a report to the Empire Rheumatism Council in England, stated that his investigation did not support this claim since in forty-eight selected patients representing ... ment was ob-

worth in an adequately controlled series of cases in any of the affections.

Spinal "Pumping."—Gillman and Gillman (1946), in Johannesburg, have recently reported a series of cases of acute and subacute rheumatic fever in which they oftentimes observed spectacular amelioration of symptoms following one or more bouts of spinal "pumping" according to the method of Speransky. In essence, this method consists in the introduction of a spinal puncture needle just within the subdural space, the attachment of a 10 cc. syringe, and then the very slow withdrawal and reinjection of 10 cc. of the spinal fluid about twenty times At the conclusion of the bout 10 cc. of fluid are withdrawn as the needle is brought out. The reactions to this treatment seemed to be quite severe in practically all cases and there was one death

PROPHYLAXIS

Hygienic Measures.—Morgan (1945) stressed the fact that easy fatigability, listlessness, restlessness in sleep, unexplained bouts of fever, and failure to gain weight properly—all of these symptoms being usually exaggerated in damp or rainy weather especially in the spring of the year—are not sufficient symptoms upon which to base a diagnosis of rheumatic fever but that they do justify the belief that the child has a favorable soil in which the disease may become implanted. Such children, especially during the most susceptible age period of seven to thirteen years, should be kept under careful observation and have all foci of infection removed; they should be guarded against infections and be given long periods of bed rest after any bouts of illness.

Since it is extremely important that the rheumatic individual in a quiescent phase of the disease be protected against sore throats and colds that may be

infections of the upper respiratory tract, and of exposure to crowds during epidemic periods. Whenever even the least degree of respiratory infection develops in the patient he should promptly be put at complete bed rest, and

and minor operations may also precipitate attacks, the life of the rheumatic patient is at all times to be maintained on as even keel as possible. And all of this is to be done while attempting to avoid the development of an inferiority complex in the child!

Suitably controlled experiments performed during War II demonstrated the possibility of reducing the dissemination of respiratory diseases through disinfection of the air in closed occupied spaces; such activities might be expected to lower the incidence of rheumatic attacks since they are so often initiated by pharyngeal and upper respiratory infections The means employed are dust-suppressive measures, ultraviolet irradiation, and the use of the germicidal

matic fever patient though far from curative and that treatment in sanitariums

which the whole family can readily be moved or in which the affected person is of an age and temperament permitting transfer without engendering a feeling of being exiled. They pointed out that such transfer to be truly effective must be essentially permanent since the transferee escapes the provocative infection only so long as he remains in the [illegible]

Mass Employm[illegible] mides to check dis[illegible] occurrence of numerous entities of proved or presumed streptococcal origin, including rheumatic fever, had ample trial in the Armed Forces during War II here in the United States. Coburn (1944), reporting on the continuous ingestion of 15 grains (1 gm.) of sulfadiazine daily by 30,000 men at three Naval Stations during five months in the winter and spring of 1943-1944, stated that this prophylactic measure was almost 85 per cent effective in preventing implantation by *Streptococcus hemolyticus* and that approximately 85 per cent of the expected rheumatic fever cases appeared to have been eliminated by it. Holbrook (1944), reporting a similar experiment in the Army, stated that there was a 50 to 75 per cent reduction in the incidence of respiratory diseases and streptococcic infection and that the reduction in the occurrence of rheumatic fever cases seemed to parallel that of the respiratory and streptococcic diseases. It was certainly a fine thing for the war effort that all of this illness was saved by the daily ingestion of sulfonamides over a long period of time by [illegible]

in a trainee group during War II; there was a prevalence in this group of hemolytic streptococcal strains showing *in vitro* resistance to sulfadiazine and possibly derived from strains that had acquired resistance during the preceding periods of chemo-prophylaxis that had been instituted in the training school.

Individual Employment of Sulfonamides.—A much more rational measure than the above is the attempt to prevent recurrences of active rheumatic fever in individuals who are in a quiet state after one or more bouts of the disease. To attempt to maintain a certain blood concentration of the sulfonamides in such persons, who are already sick individuals, seems to be entirely justifiable and rational Indeed, since the reports of Thomas and France, and of Coburn and Moore, both of which appeared in 1939, there have been many recorded experiences with this sort of thing. Rosenberg and Hench (1946), in summarizing all of the reports that had appeared at the time of their writing, found the following: (a) among the rheumatic patients protected by sulfonamides during 1037 seasons, only twenty-two acute rheumatic exacerbations occurred (an incidence of 2.2 per cent) and only three patients died from rheumatic fever. Among the patients not so protected during 1340 seasons, there were 183 acute attacks (an incidence of 13.7 per cent) and five deaths from rheumatic fever. In short, among the rheumatic patients not protected by sulfonamides there were six times as many acute recurrences and almost twice as many deaths as [illegible] lfonamide

[illegible] have

[illegible] ghtly

active in order to protect the patient against possible carriers of hemolytic streptococci, but because sulfonamides sometimes severely accentuate the symptoms of an acute attack most investigators have refrained from starting sulfonamide prophylaxis until four to six weeks after all signs of activity of the latest rheumatic attack have disappeared.

Season.—Most patients have been treated only from October until June, but it seems to me that continuous administration throughout the year, as advocated by Thomas (1944) and others, should be preferable since such a procedure would not only afford a more complete year around protection but would likely minimize the occurrence of drug sensitivity resulting from interrupted dosage.

Choice of Drug.—In most reports to date sulfanilamide has been chiefly employed, but Rosenberg and Hench (1946) said that at a government conference attended by specialists in the rheumatic disorders sulfadiazine was considered preferable to sulfanilamide, it was also said that sulfamerazine was regarded as potentially the sulfonamide of choice because its relatively slow excretion might enable an effective blood level to be maintained on one small daily dose.

Dosage.—Usual adult dosage has been 15 to 30 grains (1 to 2 gm.) daily, divided into three doses at eight-hour intervals or two doses at twelve-hour intervals, the dosage most employed for children has been 7½ to 15 grains (0.5 to 1 gm.). Most workers have felt it satisfactory to attempt to maintain a blood level of 1 to 3 mg. per cent.

Toxic Reactions.—It certainly seems that no great risk is incurred by the employment of this type of prophylaxis since in the various series of reported cases the incidence and degree of reactions have been usually stated in some such words as "infrequent and unimportant"; in the record of the 1037 patient [illegible]

once or twice weekly during the first four weeks of treatment, and thereafter at least once monthly.

Duration of Sulfonamide Prophylaxis.—How long the average individual may be dosed in this way with impunity is of course not yet determined, but Thomas (1944) mentioned a patient who had taken prophylactic sulfonamide successfully for nearly eight years. The opinion has been expressed that administration of the drug should be continued at least eight years or, in the case of a child, until the age of sixteen is reached.

Adverse Criticism.—Wilson and Lubschez (1944) determined the rates of recurring attacks in their own cases not protected with sulfonamides and compared them with the rates in a number of the published studies on sulfonamide prophylaxis. In four of five reports thus examined they found the observed number of recurrences among the sulfonamide-treated patients not significantly lower than the expected number, and they consequently expressed the belief that conclusions on the efficacy of the chemo-prophylaxis of rheumatic fever should not be drawn from such studies. However, Rosenberg and Hench submitted the controversy to an experienced medical statistician who concluded, it seems, that such summations of the data as theirs [illegible]

trolled to make any conclusions therefrom valid, and Taran (1947) seems to be in agreement with her.

Penicillin.—Now that the oral administration of penicillin has become feasible the time is certainly ripe for a large scale study of its value in the prophylaxis of rheumatic recurrences. Burke's (1947) small scale study, in which he was able to assess the findings on clinical grounds alone, certainly offered a hopeful indication of what may be revealed by a larger study. Burke divided a group of twenty persons, who within the previous twelve months had had acute rheumatism preceded in every case by a pharyngeal infection, into two groups of ten matched as closely as possible with regard to age, sex, occupation and clinical condition. The individuals in the treated group, composed of three school children, two housemaids, two farmers, two laborers and an ex-sailor, their ages ranging from eleven to twenty-nine years, were given three lozenges daily of 500 units of calcium penicillin, being instructed to dissolve the lozenge slowly between the cheek and lower gum and to swallow the saliva containing the penicillin in solution. One lozenge was used on awakening in the morning, another before lunch, and a third on retiring at night. The treatment was continued for twelve months, during which time the ten patients in the control group received no special treatment beyond ordinary precautions against overcrowding, fatigue and exposure. At the end of the year it was found that rheumatic manifestations had been five times more frequent, and throat infections six times more frequent, in the control group than in the treated group.

Salicylates.—It does not seem to me that the attempt to prevent recurrences of rheumatic fever by the administration of salicylate has got very far. In the most recently reported study, Coburn and Moore (1942) gave 60 to 90 grains (4 to 6 gm.) daily for one month to rheumatic patients developing pharyngitis and in whom Group A hemolytic streptococci were cultured from the throat. Forty-seven patients were treated and 139 were held as untreated controls; among the latter, fifty-seven developed recurrences of rheumatic fever, giving a percentage of 41, whereas in the treated group there were only sixteen recurrences, giving a percentage of 34. To be sure, it was said that only one of these patients in the treated group developed rheumatic fever and the other fifteen only showed a brief asymptomatic rise in the sedimentation rate, but since it was not stated how severe the recurrences were nor what the criteria of recurrence were in the control untreated group, it does not seem to me that this report supplied very clear-cut evidence in favor of salicylate prophylaxis.

Immunization.—Through the years the attempts to immunize patients by the employment of various streptococcal vaccines have come to nothing. To be sure, a recent report of Wasson and Brown (1943) was favorable, but much confirmation and extension of this work will have to be made before it will seem advisable to describe it as a practical measure here. In the summer of 1944 at the Naval Training Center, Farragut, Idaho, *Streptococcus pyogenes* infections became epidemic, the majority of the infections being caused by Group A, Type 17 and 19 strains, resistant organisms that are not affected by sulfadiazine prophylaxis. During this outbreak an attempt was made to control such infections by type specific inactivated streptococcal vaccine; the attempt failed.

Dietetics.—As a result of their study of the dietaries of 100 rheumatic children, Coburn and Moore (1943) felt that they found indications of a close

association between
subjects having poo
consistently low in
ficient in so many f
portance of any one factor
as a result of his study of
pared with those of twent
correlative heads culled from the literature, concluded that rheumatic fever closely follows the incidence of clinical rickets, which latter in his opinion probably alters the individual's immunity to the infective organism; he therefore logically concluded from his premises that the importance of adequate amounts of vitamins A and D, milk, protein, and the value of sun bathing cannot be overemphasized in the prevention of rheumatic fever. Possibly Peete is right but it will take a great deal of work to prove the point

Tonsillectomy.—Very few
even fatal flare-ups in quiesc
with tonsillectomy I think th
students of this matter until someone produces incontrovertible evidence that children without tonsils are definitely protected against rheumatic routine tonsillectomy is not justified but when the
and septic (but not merely
glands, the removal of ton
Wilson (1940), summarizing her own data and that supplied by that the evidence does not lend support to the view that
per se is an indication for the removal of the tonsils
tonsils does not insure against future streptococcal in
(1942) emphasized, much lymphoid tissue is left in th
is now appreciated that streptococcal rhinitis may be
cursor of rheumatic fever as is streptococcal tonsillitis
cates the advisability of giving large doses of penicillin
prevent subacute bacterial endocarditis when tonsillect
indicated

Tooth Extraction.—Sometimes the extraction of a to
individual seems to precipitate him into subacute
Of course if the tooth must come out it must, but it
that its removal may be a dangerous procedure The
in these cases as in tonsillectomy (see above) seems

RHEUMATOID ARTHRITIS

(Chronic Infectious Arthritis, Proliferative Arthritis, Atrophic Ar

changes involving primarily the synovial membra
joints, great pain and tenderness and limitation of
joint to joint, and enough new growth of fibrous
cause
a spin
and sh

atrophy takes place In many instances the attack is preceded by anorexia, easy fatigability, weight loss, vasomotor disturbances and other evidences of constitutional involvement; *during the attack* there is often low-grade fever and nearly always an increased sedimentation rate, the latter usually proportional in degree to the severity of the involvement Ankylosis, which is very common in this type of arthritis, usually does not appear until after the patient has suffered [illegible]

[illegible] destruction of the articulating surfaces with telescoping of the joints and ulnar deviation of the hands and fingers, is now included as merely a very severe grade of rheumatoid arthritis In a book of this limited scope it must suffice to consider the following relatively rare maladies as merely unusual forms of rheumatoid arthritis: Still's disease, chronic infectious spondylitis, Marie-Strümpell syndrome, Felty's syndrome, von Bechterew's syndrome.

This may possibly be an infectious disease, but as yet neither the hemolytic streptococcus nor any other specific bacteriologic agent has been indicted in the causative role Like rheumatic fever, rheumatoid arthritis is encountered only in a "spotty" distribution in the warmer climates and the incidence is higher among the poor than among the well-to-do Further indication of the possible relationship of these two diseases is to be found in the necropsy studies [illegible]

Rogen (1947) was able to elicit clinical evidence of mitral valve disease in only one patient in a series of thirty-three cases of rheumatoid arthritis, though he recognized the possibility that the incidence of subclinical valvular disease might be much higher than this. It certainly seems that the fact of a direct relationship of rheumatic fever and rheumatoid arthritis is not yet established The careful study of Cobb *et al.* (1939) caused them to feel that grief and family worry, in addition to poverty, bear more than a chance relationship to the onset and exacerbations of the disease; indeed there is an increasing group of observers who look upon the arthritic phenomena as representing a psychosomatic reaction Evidences of an hereditary factor and of a predisposition to develop rheumatoid arthritis seem to be increasing as our knowledge grows Differences in racial susceptibility are not pronounced though somewhat fewer Negroes are affected than whites There is still much confusion among students of this malady. Some point to the frequency of constipation and the low gastric acidity of many of these patients and consider that these things are of at least great contributory importance, decreased functional capacity of the liver is also alleged to be a frequent occurrence Others cite hypothetic metabolic [illegible]

tance of none of these things has been proved. The belief that the disease *is* initiated from some primary focus of infection in the teeth, tonsils, sinuses, gallbladder, cervix, prostate, colon, or elsewhere nowadays no longer holds the forefront of attention. The observation that arthritis may recede before pregnancy has been made a number of times, but it was only a few years ago that Hench recorded the actual occurrences in a series of patients Twenty of the twenty-two patients experienced striking, generally complete relief *during*

of what is practiced in other inflammatory conditions, in which physiologic rest is always enjoined; therefore it is wrong, and what is truly indicated is to immobilize these joints, even with plaster casts if necessary, during the acute stage Thus muscular spasm for the protection of a sore joint, with the resultant flexion deformity, is prevented. Complete relaxation and total body rest will take place, too, when the patient knows that his every movement will not be painful. (b) The use of a firm bed must be insisted upon even though this firmness can be obtained only by placing a 1-inch board directly beneath a "hard" mattress, for only thus can gross deformities be avoided in severe cases. (c) Fibrous adhesions apparently need not be feared if the cast is split in two days and daily passive motion is instituted and further fixation is continued or not, as the daily expert observation dictates. Even after the joints are entirely freed from splints during the day, the latter should be used to make full rest and sleep possible at night. (d) When to start massage and exercises, and how much exercise can be given? "During the acute phase, if an overzealous physician or even a brave patient, fearful of impending deformities, should attempt to start motion prematurely, nature's warning of severe pain and increased spasm generally prevents The patient holds the joint as still as possible, and nature begs for help in making that rest absolute. But soon the patient will involuntarily at first, then under encouragement, warily move the joint a little. That is the signal for institution of light massage and very gentle, passive motion As the subacute stage fades into the chronic stage, pain and tenderness further subside, and active and passive motions are increased. The rules of exercise are relatively simple Any exercise that does not produce pain either during its administration or afterward is harmless, and can be persisted in as long as it remains painless. Any exercise that hurts the joint slightly while it is being carried out but produces no appreciable 'hang-over,' and is not followed by a significant increase of pain, is safe However, exercise should be avoided which, whether it produces immediate pain or not, is followed by a hang-over, such as increase of pain that day or the next" The reason for massage is the hope of improving the circulation in the joints and neighboring parts and preserving muscle tone Naturally, not just any "rubbing" will accomplish these things, nor is any one professional masseur as good as another, some of them are much too enthusiastic and do more harm than good in the beginning The best procedure is to have the work started by a technician who has been properly trained by an orthopedist, and then after a while have some member of the family attempt to take over this work if she can develop the knack (e) The correction of deformity in the quiescent stages of the disease by manipulation and mechanical stretching, by manipulation under general anesthesia, or by open operation, is a measure in which orthopedic surgeons have made great strides in recent times, but of course the indications or procedures cannot be described here The correction of faulty [illegible]

is increased instead); to promote circulatory improvement through the induction of hyperemia; and to cause the patient to sweat (we do not know why this

is very low, particularly in bed-ridden patients, and the danger of addiction minimal; however, demerol *is a drug of addiction* and it seems to me that the advisability of its employment in rheumatoid arthritis is therefore very questionable. Physical therapeutic measures have a considerable though often temporary analgesic effect. Short and Bauer (1942) felt that further trial should be made of the injection of 2 per cent procaine solution above the affected joint, for they said that at times the temporary relief which this affords is held and the vicious cycle of pain, muscle spasm and disability is apparently broken for awhile Some years ago Waugh introduced intra-articular injection of lactic acid with procaine, and Mawson (1946) has used this treatment with considerable success in twenty-six cases of mixed forms of arthritis, including some cases of rheumatoid arthritis and some of osteoarthritis. From 15 to 20 cc. of a stable solution of 0.2 per cent lactic acid with procaine, having a pH of 5.2, is injected into and around the hip joint or into the knee joint; it seems that the wrist joint will take only from 2 to 5 cc. Crowe (1947) injects into a painful hip joint 20 cc. of 1 per cent acid potassium phosphate in isotonic saline solution; two or three weeks later 10 cc. of acid magnesium phosphate solution is injected and thereafter the intervals of injection are spaced in accord with the tendency to relapse; it is said that usually six or eight injections are sufficient. In 1944, Crowe stated that he had accomplished the relief of pain in three-fifths of 280 painful joints so treated.

"Building-Up" Therapy.—Most rheumatoid arthritics are of the lean and scrawny type, many of them are grossly underweight and hypochromic anemia of some degree is practically a constant finding. Certainly it is rational practice to try to "build up" such people and would be even though they did not have arthritis. But we have as yet no magic wands that are worth the waving. All the present pother about vitamin stuffing is still just pother Hench (1946) subscribes to the belief of others that there are no direct indications for the use of vitamins A, C, E, K and B complex for the relief of symptoms in rheumatoid arthritis. The value of high vitamin D preparations such as ertron has not been proved to the satisfaction of many men not fond of wishful thinking, but there can be no doubt of the potential toxicity of these agents The study of Bayles *et al.* (1943) of the dietary history of thirty-one patients with rheumatoid arthritis, for the year before the definite onset of their disease process, revealed that their food intake was essentially the same as that of a cross section of families in the North Atlantic states, and it would seem [illegible] contributory to the onset [illegible] creased total requirement [illegible] in his average diet. In treatment, so far as we are as yet aware, the patient needs only a good nutritious diet. Unfortunately the anemia is not usually easily corrected with either iron or liver preparations. Transfusions seem to be many times helpful in the early active cases and sometimes also in [illegible]

[illegible]

Swaim, Holbrook and Hill, Stump and Krusen are among the [illegible] [illegible] to the nonspecialist [illegible] that to "keep going" [illegible]le is quite the reverse

pain in his head, his sides and his feet has come from his teeth; they must be extracted" N

he is sure to l

But why—if

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Occasionally, to be sure, the response is startling and there is a case to report and moralize upon, but it does not happen with any great frequency; and sometimes an exacerbation is unquestionably initiated. It now seems to be the consensus that in "eradicating" a focus we do not always get rid of the bacteria anyway, for they often continue to live and multiply in the tissues surrounding the area from which the "focus" was removed Reimann and Havens (1940), in a critical appraisal of the entire subject of focal infection and systemic disease, were unable to make out a case in favor either of the theory or of the routine "eradications" based upon it, and since the appearance of their paper no one has effectively taken up the defensive cudgels in the matter.

Gold Therapy.—It seems to me only fair that the reader be apprised of the cause of the renewed interest in gold therapy in our country. A good many years ago the French began using gold (to their own satisfaction at least) in tuberculosis and since they feel there is probably an association of some sort between tuberculosis and rheumatoid arthritis, they logically tried gold in the latter also. Forestier was the outstanding leader in this work who, after numerous publications detailing successful employment of gold, came to this country and lectured on the subject. There followed a number of trials of the agent by American clinicians, but the reactions were so frightening that gold therapy was quickly abandoned here But the French and others on the Continent continued to report their satisfaction with the remedy and then the British took it up. But we still held off and finally the British lost patience with us and editorially as well as during personal visits to our shores let us know they thought we were not giving a good agent the fair chance it deserved. Of course had real "foreigners" pursued such tactics with us the result could only have been a strengthening of our opposition, but when friends with whom we have traditional ties in medical and many other fields so persistently nagged us it was only natural that here and there a clinic director said in effect "Oh, all right," and began a new study of the drug.

Efficacy.—There are now available in the American and British literatures

only state here that in an authoritative and conservative report presented by Ragan and Tyson at the 1946 meeting of the American Rheumatism Association, it was stated that of 142 patients treated with gold, 50 per cent had shown objective improvement on one or more courses, 13 per cent maintaining their improvement for at least three years Such results are certainly not impressive, for Short *et al.* (1946) were able to record that 53 per cent of a series of 274 arthritic patients treated in the Massachusetts General Hospital experienced more or less satisfactory improvement upon nothing but general and orthopedic therapy. Hench (1946) says that notable results with gold are achieved in only 20 to 35 per cent of cases, but he believes this type of therapy to be justified whenever rheumatoid arthritis has lasted more than a few months and shows evidence of being progressive, provided that the patient

world knew that a cure for syphilis was at hand

Dosage—Of the three salts most used in the United States, sodium-gold-thiomalate (myochrysine), sodium-gold-thiosulfate, and gold-thioglucose (solganol B.), only the thiosulfate salt may be given either intravenously or intra-

weeks, to be followed by one or more similar courses. But Hench (1946) notes that because gold salts accumulate notably in body tissues when weekly doses of 100 mg are given, the current trend is to employ smaller dosage than formerly. Ragan (1946) starts with doses of 10 mg, increases to 25 mg. and if tolerated to 50 mg at weekly intervals, and continues at 50 mg weekly until the patient has received 1 gm of the compound If improvement has been shown and there has been no untoward toxic reaction the gold is continued at 50 mg. every two or three weeks, being discontinued at the onset of any toxic manifestations Depending upon the severity of the toxic reaction the gold may be given again in smaller amounts or not resumed at all. Cecil (1946) says that in very mild cases, or in patients suspected of being sensitive to the drug, a maximum dose of 25 mg is not exceeded and that in only rare instances where 50 mg doses fail are 100 mg. doses used, he says that they really have no fixed amount for total dosage at the New York Hospital Coss' (1946) initial dosage in children is 3 to 5 mg, increased to 25 mg, 600 mg. usually constitutes his course but some very young patients have been given no more

temporary *increase in pain, skin eruptions, exfoliative dermatitis, edema,*

toxic reaction than is a patient recently come down with the disease Cecil (1946) says that with vigilance gold therapy is "fairly safe" But significant

and Leichtentritt (1943), 42 per cent of those of Rawls *et al.* (1944), and 8.9 per cent (single course) and 15.6 (two courses) of those of Cohen *et al.* (1945) Short's (1942) review of the reported cases in the literature showed that 1 in 200 (0.5 per cent) of the patients given gold dies as a result of the injection Coss and Boots (1946) said that in their experience gold therapy was no more dangerous in children than in adults, and I suppose this is something to be thankful for, but to me, reviewing the matter from the side-lines, the agent does not seem to be one that is even "fairly" safe. The recent papers of Cohen

Contraindications.—The principal ones seem to be the following: pregnancy,

a complicating psoriasis respond less favorably), active tuberculosis, hyper-

Australia, considered that thin anemic patients with cold clammy skin should

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reports were not sufficiently critical and stated that at a meeting of the American Rheumatism Association several experienced rheumatologists expressed their disappointment with this type of treatment and their belief that prostigmine was of little or no value in rheumatoid arthritis. One can easily agree with the viewpoint recently freely expressed that if one is to use a drug so potent as prostigmine it should yield much more definite benefit than anyone has observed with this drug in rheumatoid arthritis to date. Cohen *et al.* (1946), who introduced the use of prostigmine in 1944, have now proposed its abandonment and the substitution of physostigmine therefor, the latter agent in their hands causing less local pain and no severe toxic reactions Their usual procedure is to give $\frac{1}{100}$ grain (0.6 mg.) each of physostigmine salicylate and atropine sulfate simultaneously; if no relaxation of muscle is obtained the physostigmine is increased to $\frac{1}{50}$ grain (1.2 mg), the dose of atropine being increased or decreased depending on the reaction encountered If the patient complains of dizziness, salivation, pain in the abdomen or nausea, the dose of physostigmine is reduced or the atropine increased as the case might be.

Nicotinic Acid (Niacin).—Kurtz and Orth (1946) employed this vasodilating

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rate that flushing was just maintained; the initial injection was ... per cent solution in physiologic saline and was usually given during sixty to ninety minutes. If this was well tolerated 400 cc. of the same concentration was given daily thereafter, but if the patient developed a visible flush lasting less than an hour, or if he became tolerant to the drug, the strength of the

solution was increased to 0.1 per cent. Ultimately one patient required 400 cc. of 0.8 per cent solution daily to obtain a satisfactory flush. After completion

return to hospital the daily intravenous injections were resumed. If the individual could not be hospitalized he was given three intravenous treatments weekly plus oral medication two or three times each day, fewer oral administrations being taken on the day of the intravenous treatments The most satisfactory method of giving nicotinic acid orally appeared to be every fifteen minutes for three doses before breakfast and again later in the day, either

therapeutic responses were made by a large proportion of their patients, this niacin method of treatment had not been used long enough at the time of their report for the results to be considered as anything more than preliminary findings Evaluation on both a subjective and an objective basis was attempted in all cases; subjectively a greater proportion of patients responded than was

adequate trial and have been found to be of no value.

Induced Jaundice.—Many men have observed that when the victim of rheumatoid arthritis develops jaundice there almost invariably occurs a re-

of 312 volunteer patients whom they inoculated with material from cases of acute infectious hepatitis or with icterogenic serum. All of the patients were kept under observation for six months, during which time only two of those who failed to develop jaundice had a spontaneous remission whereas ten of the thirty-two who were successfully inoculated became completely free from pain and fifteen showed some improvement. The remissions were unequal in degree and of short duration, the average period during which optimal im-

the experimental animal through the injection of a crystalline bilirubin plasma mixture, if this work can be successfully carried over into the human it may be that we shall have available a method of inducing jaundice in man with little or no risk

X-ray Therapy.—Since in the treatment of spondylitis rhizomélique roentgen therapy is frequently of value it might be expected that it would be useful also in the treatment of rheumatoid arthritis of the joints of the extremities, for the pathology of the spinal and extremity joint inflammation seems to be identical. However, Smyth *et al* (1941) put the matter to a thorough test in rheumatoid arthritis, studying the effects from the standpoint of subjective and objective changes and also through frequent sedimentation rate determinations and diagnostic x-ray examinations of the joints. The results were so unpredictable and unreliable that they decided to abandon this type of therapy except in rare obstinate cases "or cases in which a psychic effect is desired" Freyberg (1946), of this same group of observers, while noting that Borak and Taylor (1945) had obtained better results with a different technic, felt that the most important theoretical and practical criticism of roentgen therapy of the diseased joints in cases of rheumatoid arthritis is that it is local treatment administered for a constitutional disease; he said that with the passage of more years following their original report their conclusions remained the same.

Antireticular Cytotoxic Serum (Bogomolets).—This subject is dealt with in Acute Rheumatic Fever.

Climatic and Spa Treatment.—Occasionally in rheumatoid arthritis, though much less often than in osteo-arthritis, the patient will be benefited, psychically if not otherwise, by a trip to a spa, but unfortunately the economic strain of such a sojourn cannot be borne by the majority of individuals Likewise, those who can move permanently into a warm climate, not necessarily dry, may be benefited if the malady is not too far advanced, but see *Change of Climate* in Rheumatic Fever.

Employment.—Some years ago Coulter pointed out that occupational therapy can be applied at home if the patient, physician and family will earnestly set about finding tasks which will provide opportunity for the repetition of exact motions—for example, for bending and straightening the leg at work while the patient is thinking about his job, he suggests refinishing wooden furniture, which involves constant squatting and rising as the rungs and other parts of a chair are worked upon. How to return each crippled individual to a job in which he can regain economic freedom at a cost to his self-respect that is not excessive is a problem indeed, but the physician must help bear the burden of trying to solve it.

Palindromic Rheumatism

In 1940 and again in 1944, Hench and Rosenberg reported their observation of a new syndrome to which they gave the name palindromic rheumatism, which seems to mean merely recurrent rheumatism. In this malady there are brief recurring attacks of pain, swelling, tenderness and redness in or about a joint, without fever or other notable evidences of constitutional disturbance, often with marked temporary disability but invariably complete recovery and no permanent injury to the joint The attacks start very abruptly and usually last only from a few hours to a few days though in two of the thirty-four cases of Hench and Rosenberg the symptoms sometimes persisted for two to three weeks. In some of the patients attacks occurred almost daily, in some they

came at intervals of several weeks, and in others there were long intervals of freedom up to six months In the thirty-four patients the average duration of

into the joint cavity and localized periarticular swelling; fibropurulent exudate in the joint cavity and acute inflammatory reaction in the synovial membrane

only laboratory findings during any of the attacks were relative lymphocytosis and moderate transient increase in the sedimentation rate.

In these cases of Hench and Rosenberg the attacks seemed to bear no relationship to acute infections, and removal of what foci of infection could be discovered did not affect the disease. Vaughan (1943) reported ten cases of food

rheumatism to include nearly related syndromes such as intermittent hydrarthrosis and certain rare and more complicated syndromes, inclines toward the allergic hypothesis

THERAPY

Hench and Rosenberg tried a good many measures and had success with none of them. Hopkins and Richmond (1947) made the trenchant point that, while nothing can be done in the way of effecting immediate relief in these cases, it is very important that the nature of the malady be recognized for it then becomes possible to assure the patient that he will not suffer joint deformities.

OSTEO-ARTHRITIS

(Hypertrophic Arthritis, Degenerative Arthritis)

This is the type of arthritis characterized by the presence of Heberden's nodes and the gradual onset, in individuals in or past middle age, of stiffness and limitation of motion, some muscle spasm and pain which may be both localized and radiating or referred There is degeneration and thinning of the cartilage with new growth of bone around the edges of the joints involved, principally the spine, knees, knuckles, hips and shoulders, but without fusion of the articular surfaces, i.e., bony ankylosis and flexion deformity do not occur in osteoarthritis and it is altogether a less virulent-seeming malady than rheumatoid arthritis In further contradistinction to rheumatoid arthritis, which is a disease of the synovial membranes and possibly infectious, this is a non-infectious disorder of cartilage and bone Very likely it is merely one of the phenomena of senescence, symptoms developing only when a joint that is wearing out continues to be subjected to chronic trauma; it has been alleged that the state is seen most frequently in the laboring classes but I do not know that a careful study would prove this to be true. Apparently osteo-arthritis may

occur as the result of an acute traumatization of a joint. Another form is that [illegible] enopausal arthritis," in which women at the [illegible] this occurs normally or after castration, have [illegible] ymptoms known as arthralgia. In this menopausal type, if the woman grows suddenly excessively stout it may be that pain and stiffness is experienced only in the knees when they are obliged to support this unwonted weight, but the symptoms are oftentimes present in other joints as well.

Osteo-arthritis is the oldest disease of which we have indubitable record—in the skeletons of beasts that preceded man on the earth by several hundred millions of years, in the "ape-men," in earliest man, in man through all the ages.

THERAPY

Most of the victims of osteo-arthritis growl a bit but do not really seriously complain of their symptoms, and in many patients—this is especially true in the menopausal cases—measures directed toward reduction in weight constitute the chief therapy. Latterly, the increasing use of estrogenic substances is giving relief in some of the menopausal cases (see article on the Menopause); Greenblatt and Kupperman (1946) think that in cases following castration by [illegible]

combined with suitable rest; he also finds it almost specific for relief of pain, promotion of absorption and restoration of function in instances in which the process is localized in the spine. Freyberg (1946), under whose direction a good many patients with osteo-arthritis have been treated roentgenologically, feels that whenever some relief from pain and stiffness is accomplished it is due to the beneficial effects on the secondary fibrositis rather than on the joint disease itself. In cases of osteo-arthritis secondary to congenital anomalies, in which the hip is not only painful but there is also considerable limitation of motion, the operation of cup arthroplasty is sometimes recommended, the procedures having been developed some years ago by Smith-Petersen. Hench (1946) said that in a series of twenty-seven cases so operated upon at the Mayo Clinic the results eight months to five years after operation were good to very good in nearly half the cases. Injection of substances into the joint has been discussed in Rheumatoid Arthritis (*q.v.*).

GOUT

Though there are many variants, the classical development of gout is about as follows. An individual—in more than 95 per cent of instances a healthy robust man—is suddenly awakened in the night by a severe pain in one of his great toes, a pain that rapidly increases until it reaches almost unbearable proportions; then at about daybreak—at "cock crow," said Sydenham (1683)—great relief is more or less suddenly experienced and the patient usually falls into a heavy sleep. On awakening later in the morning he finds that the affected metatarsophalangeal joint is somewhat swollen, is red and has a glistening appearance, and that the veins around it are peculiarly distended. Throughout the day the swelling increases and the joint becomes very tender but the pain is only slight or may be entirely absent. Then with the night comes a recurrence of the torture. Usually an attack

lasts only a few days but there occasionally occurs prolongation for a period of several weeks; not infrequently the process shifts from one great toe to the other or to some other joint, or both toes are affected at the same time, or some joint other than that of a great toe is first affected; the more rarely affected joints are the hips, spine, sternoclavicular and shoulder. A slight rise in temperature is usually noted, and sometimes an attack is preceded by spontaneous diuresis. Upon subsidence of the attack, the affected joint is completely restored both in appearance and function. The patient will then be symptomless for a period of months or years—the average time is about one year—whereupon the second attack is experienced. Thereafter, attacks occur with increasing frequency until a state of chronic gout is reached. This is characterized by marked swelling and deformity of the joints due to the gradual deposition of sodium monourate in the cartilages and ligaments. Strange to relate, it is usually not the toes that are thus involved but the joints of the hands and elbows most frequently, the olecranon and prepatellar bursae may also be distended with nodular masses. There is relatively little pain when this chronic stage is reached. In addition, in many instances tophi, which sometimes ulcerate, appear in the skin, most characteristically in the fleshy lobe of one or both ears. from these tophi the needle-shaped crystals of sodium urate may be obtained to clinch the diagnosis.

In the series of 100 cases, studied by McCracken *et al.* (1946), the average age at onset was 46 8 years, there having been fourteen cases between the ages of nineteen and thirty years, twenty-one cases between thirty-one and forty years, thirty cases between forty-one and fifty years, twenty-eight cases between fifty-one and sixty years, and seven cases between sixty-one and seventy-three years

Gout is apparently associated with a faulty uric acid economy, but the exact nature of this association is not understood. Uric acid is a normal constituent of the blood and the urine, but in gout the amount in the blood is almost always abnormally high and in the urine abnormally low; however, this alone is not sufficient to account for the development of the clinical picture, for the same conditions obtain in other diseases, namely chronic nephritis and leukemia, without gouty symptoms appearing Furthermore, the substance is not itself highly toxic since it may be quite freely injected intravenously. In favor of tl[illegible] belief in the direct relationship of uric acid to the disease is the fact that [illegible] considered beneficial in treatment, and that a diet low [illegible] increase the amount of uric acid [illegible] symptoms; Lockie and Hubbard (1935–39) proposed [illegible] diet as a diagnostic aid in doubtful cases. Most clinicians hold that som[illegible] other, as yet undiscovered, agent is at work in the causation of the diseas[illegible] allergy and a disturbance in the vegetative nervous system have both bee[illegible] p[illegible] In only 18 per cent of the American cases of McCracken *et* [illegible] [illegible] history of gout in the family, but the indicati[illegible] [illegible] in some series, witness the posit[illegible]

[illegible]

some years [illegible] excessive use of alcohol have [illegible] predisposing importance In twenty-six of the [illegible] was considered frequent and excessive an[illegible] (1946) the alcoholic intake was stated to be moderate. Overeating is also [illegible] another twenty-eight it was stated to be moderate.

corded an important role in causation, and indeed in the 100 cases of McCracken *et al.* (1946) obesity of a degree sufficient to warrant comment was present in forty-one instances. Many cases of gout seem to be in some way associated with lead poisoning and in other instances it appears that a brief period of dietary or bacchanalian excess or of physical stress or strain, or the subjection to a major surgical operation, or the taking of an unusual drug, precipitates the initial attack. Hebrews seem particularly prone to develop the disease; Negroes are rarely affected. Patients do not die of the symptoms of gout that we are so far able to recognize, but in the early stages they suffer greatly and are severely crippled later on. Gouty nephritis (the study of Coombs *et al.* 1940, indicated that the changes are the result and not the cause of the metabolic dyscrasia) and renal colic from urate stones or gravel are recognized complications and there is strong suspicion of a greater frequency of vascular diseases in gouty than in non-gouty individuals

The distribution of the disease, both as to time and place, is very interesting. Gouty deposits have been found in the predynastic mummies of ancient Egypt, and in classical times gout was very common in Greece and Rome, but at the present time the Mediterranean lands know the disease hardly at all. In the tropics of both hemispheres, as well as in China and Japan, it is extremely rare. England has suffered from gout for centuries, but it now seems to be quite rapidly decreasing there, on the Continent, too, it is said to have decreased markedly since War I. It has always been looked upon as of extremely rare occurrence in the United States, but recent studies indicate that far too many of our cases are being bandied about for many years with an incorrect diagnosis of rheumatoid or osteo-arthritis, or a mixture of these two.

THERAPY

The Acute Attack

At the height of the acute attack it is usually advisable to give a full dose of morphine or dilaudid in order to bring quick relief from the severe pain. At the same time the first dose of one of the analgesic drugs should be administered, many men also give a dose of cathartic salts at this time.

Colchicine.—This agent, in the form of the crude drug, has been used since time out of mind, indeed Lockie (1939) said that it is mentioned in the Ebers Papyrus of 1550 B.C., but we have not the least notion how it works; it does not affect the uric acid level of either the blood or the urine. The old galenical preparations, the wine and the tincture of colchicum, are no longer used, but colchicine is looked upon by most men of experience as being a practically specific agent for relieving the pain of acute gout. The experience of Lockie is typical though it is greater than most men have had: in seventy-five private patients with proved gout all experienced marked relief from this drug in about the time [illegible] causes set in

McCracken *et al.* (1946) [illegible]

in thirty-seven, pain be[illegible]

1/60 grain (1 [illegible]

grain (0.5 to 1 [illegible]

the taking of [illegible]

every two or three hours [illegible]

is relieved or some gastro-intestinal disturbance appears. He says that having learned his "diarrhea dose" a patient may sometimes obtain a satisfactory effect in a subsequent attack by taking somewhat less of the drug in the course Bauer and Klemperer (1944) state that the diarrhea is frequently severe enough to require treatment with a drachm (4 cc.) of paregoric following each loose stool until the diarrhea is checked; bismuth subcarbonate is also sometimes employed in addition to the paregoric. It seems that other than the diarrhea untoward effects are not caused by colchicine. Robinson (1947) says that with experience the gouty patient can often recognize prodromal symptoms and that under these circumstances three or four doses of colchicine at hourly intervals may abort the attack. Talbott and Coombs (1938) followed Cohen's practice of giving three tablets of 1/120 grain (0.5 mg.) daily for two or three days each week with satisfaction; in several of their cases colchicine had been used in this way for more than two years without the occurrence of any symptoms of toxicity.

The Cinchophens.—These drugs (discussed in detail in Chronic Gout below) are used by a few men in the acute attack in place of colchicine and they are [illegible]

Lockie's (1939) patients, too, found colchicine more effective than either the cinchophens or the salicylates But Hench champions the cinchophens (see below) These drugs increase the uric acid output when first given, but in most cases a decrease takes place after a few days, perhaps to a level lower than the previous one.

The Salicylates.—The salicylates also influence the uric acid output in a special way (see Rheumatic Fever) but it is generally recognized that they are less effective in relieving the pain of acute gout than either of the above two agents.

Nursing Measures.—Hot or cold compresses sometimes give relief but many patients are satisfied merely to keep the joint swathed in something during the attack. Bauer and Klemperer (1944) stated that as a rule diathermy is not well tolerated Absolute bed rest must be enjoined and massage and exercises are absolutely contraindicated Those who adhere to purine restriction feel that the diet at this stage should be strictly purine-free; in any case the patient should be kept upon, and indeed he will rarely desire more than, liquids and soft foods, but he must be encouraged to take 3000 to 4000 cc of liquids

Chronic Gout

Dietetics.—It has been felt by all observers since ancient times that obesity, alcohol and gout are closely associated, in our own era the fact has been ascertained that purine-containing foods increase uric acid retention, the severity of symptoms and the frequency of attacks Therefore the prime requisites in the dietary management of gout have been held to be that obesity be combated, the use of alcohol restricted and the purine content of the diet kept as low as possible consistently with a feeling of reasonable well-being Latterly, however, there are those who have begun to doubt the value of such a strict regimen as

corded an important role in causation, and indeed in the 100 cases of McCracken *et al.* (1946) obesity of a degree sufficient to warrant comment was present in forty-one instances Many cases of gout seem to be in some way associated with lead poisoning and in other instances it appears that a brief period of dietary or bacchanalian excess or of physical stress or strain, or the subjection to a major surgical operation, or the taking of an unusual drug, precipitates the initial attack. Hebrews seem particularly prone to develop the disease; Negroes are rarely affected. Patients do not die of the symptoms of gout that we are so far able to recognize, but in the early stages they suffer greatly and are severely crippled later on. Gouty nephritis (the study of Coombs *et al*, 1940, indicated that the changes are the result and not the cause of the metabolic dyscrasia) and renal colic from urate stones or gravel are recognized complications and there is strong suspicion of a greater frequency of vascular diseases in gouty than in non-gouty individuals.

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thougl [illegible]
1/60 g [illegible]
grain ([illegible]
the ta [illegible]
every [illegible]

diet for an adult (but in restricted quantities!) provided that the following articles are *omitted:*

All meats, fish and shellfish, and fowl.

Soups, since nearly all soup stocks are made from meat.

Vegetables, asparagus, kohlrabi, lentils, mushrooms, onions, peas, radishes, shelled beans (kidney, lima, navy, soy), spinach and watercress.

Cereals: whole wheat bread, oatmeal, shredded wheat and other breakfast foods made from whole grain [illegible]

[illegible]

Now in order to obtain even reasonable satisfaction on such a diet the patient will have to take inordinate amounts of milk, eggs and cheese—and finally he will rebel. When this occurs allow him an occasional bit of bacon, chicken, or lamb. Among the less harmful fish, Barborka placed haddock, whitefish and [illegible]

[illegible]

rarely happens, one should bear the following things in mind as the diet is expanded·

(a) The worst offenders among the meats are sweetbreads, kidneys, liver and brains; among the fish, sardines, herrings, anchovies, pike, cod and perch; among the fowl, squab and turkey.

(b) Boiled beef, from which the water has been twice poured off while cooking, has lost some of its purines and thereby becomes more acceptable

(c) Soups are perhaps best not used at all because of their high content in extractives.

(d) Adding vegetables from the interdicted list is less harmful than adding meats, fish, or fowl

Relative Amounts of Carbohydrates and Fat—Bartels (1943) said that indisputable benefit was obtained in thirty-one of thirty-eight patients in whom fats as well as purine-formers were restri[illegible] of carbohydrates were allowed. Certainly [illegible] regimen extended trial because Lockie a[illegible], have shown that fats tend to provoke gouty attacks. Bauer and Klemperer (1944) demur, however, because in their experience gouty attacks were not precipitated with any regularity by a high-fat intake nor did the omission of fat from the diet prove beneficial

The Cinchophens.—Many men feel that the danger of serious poisoning with the cinchophens outweighs the advantages derived from their use, particularly as the disease progresses relentlessly despite all medication anyway. However, Hench (1941) is convinced that the cinchophens are the most effective drugs available and that their use is justified except for patients with hepatic dysfunction, or idiosyncrasy for the drug, or in those unwilling to take the slight risk, but he also advised that certain precautions be taken. Here is the regimen employed by Hench at the Mayo Clinic: (a) cinchophen is used in preference to neocinchophen because it is believed to be more effective even though somewhat more disturbing to the gastro-intestinal tract, (b) the patient takes 7½ grains (0.5 gm) three times daily for three consecutive days each week and continues this indefinitely with only such

satisfaction of these requisites necessarily imposes. Bauer (1943) stated authoritatively that high-purine diets do not provoke the acute illness in latent gout with any regularity and that no correlation has been possible between the [illegible]

totaling more than seven months had twelve attacks and severe gout on twenty-seven days, while during the following eight months at home on unrestricted diet he had seven attacks and severe gout on eighteen days. Patient B during nine months in the hospital had twenty-one attacks and spent thirty-nine days in bed; in the succeeding fourteen months at home on an unrestricted diet including a moderate intake of beer and occasional indulgence in hard liquor he had seven attacks and spent only seven days in bed. I do not believe that anyone knows what to make of such things and it seems to me that at present we can still only proceed upon the basis of the low-purine hypothesis, while hoping ardently that someone soon solves this riddle for us.

Combating Obesity.—We cannot attack the problem as we would ordinarily do in obesity, *i.e.*, by greatly restricting carbohydrate and fat consumption, because this necessitates the allowing of so much protein that the patient is forced to take more of the purine-containing fowl, fish amd meats than is permissible. Therefore we can combat obesity in gout only by a constantly [illegible] Gouty individuals usually adore stuffing [illegible] arly always fail)

[illegible] drinker or the debauchee who is most prone to gout, and therefore counsel against the "spree," but as a matter of fact few drunkards develop the disease. It is the more or less steady but quite moderate drinker, especially of red wines and beer, who is likely to be gouty. For this reason total abstinence is the thing to be recommended, though I must add that Bauer and Klemperer (1944) have [illegible]

diet that would be sustaining because even the common [illegible] purine-free But the worst purine-formers are fish, fowl and meats; these should be omitted from the diet during most of the time. The total proteins need not be reduced, therefore meat, fowl and fish restriction is compensated by the use of large amounts of milk, eggs, cheese and proteins in vegetable [illegible]

acid precursors. Perhaps this is just one of those things [illegible] books without real justification; patients would be immensely relieved if the [illegible]

[illegible] ftentimes miserable enough [illegible] for a little reduction in his [illegible] only [illegible] and [illegible] free

Actual Diet in Chronic Gout.—[illegible] diet as nearly as is practicable, the patient may be permitted to eat the normal

to prevent infection. He said that thorough débridement results in t healing.

rcise.—The value of exercise for the gouty individual has been long rec-d Golf is unfortunately the only form of outdoor exercise that many en can enjoy, but the fact should not be overlooked that for individuals o corpulent and whose arteries are not yet markedly sclerosed it is ctly less valuable than the more vigorous forms of exercise It is sadly that the streets of our industrial cities are becoming less attractive to the nd less stimulating to the spirit as year follows year; still a brisk walk is a walk and as such is worth far more to an individual in need of exercise is a round of golf as played on a crowded city course.

he Spa.—Spa treatment is endeared to us of old, its value lying not in ingestion of the mineral constituents of the waters but in the taking so much water itself, plus the other elements of a complete environmental inge that renders the resorts so valuable in the treatment of many chronic isorders

FIBROSITIS

(*Myositis, Muscular Rheumatism*)

This is possibly the most frequently encountered of the rheumatoid disturbances and likely deserves a more dignified position than it has attained in the literature, for there is no doubt about the incapacitating nature of an attack of fibrositis even though it is usually of only brief duration Among 900 admissions in the arthritis clinic of the Hospital for the Ruptured and Crippled in New York, Traeger (1937) and his associates made this diagnosis in 262 instances, *i e*, patients who presented with pain in or about the joints with no external evidences of joint pathology such as swelling, redness, fluid accumulation, muscular atrophy or deformity and without roentgenologic evidence of bone pathology or any laboratory findings of an elucidating nature As the term indicates, fibrositis is an inflammatory reaction in the fibrous tissues of the body, and therefore the terms "myositis" and "muscular rheumatism" are misnomers since it is involvement of the interstitial tissues rather than of the parenchymal muscle tissues that causes the symptoms. Since fibrous tissue exists everywhere the possibilities for anatomic distribution in fibrositis are very great, but the pain, tenderness, and muscle stiffness (jelling phenomenon) which characterize it are most frequently encountered in the following forms. lumbago, torticollis or wryneck; and excruciating headache centering in the back of the neck, intermittent attacks of pain in any muscle groups associated or not with unusual use, stiffness or soreness of the joints after long periods of rest; interstitial neuritis in which the pain and tenderness are in the muscles and not along the nerve trunks; bursal fibrositis, which differs from bursitis in not being accompanied by increase in fluid in the bursa and definite limitation of motion; panniculitis, in which here is loss of the elasticity of the skin, which becomes more adherent to underlying tissues, fibrositis of the palmar fascia (Dupuytren's contrac-). In England, where trigger-points of pain and palpable "fibrositic es" seem more frequently to characterize fibrositis than here in the States, Copeman and Ackerman (1947) have performed considerable ful work resulting in the suggestion that localized areas of fibrofatty become edematous for some unknown reason and that the tension occurrence in an unyielding fibrous investment is the cause of

modifications as seem indicated in the individual case; (c) the following "precautions" are observed: patient must ingest 2 liters of fluid and liberal amounts of carbohydrate daily and take enough alkali (15 to 30 grains [1 to 2 gm.] potassium citrate or 30 to 60 grains [2 to 4 gm.] sodium bicarbonate three times daily) to prevent renal colic from precipitation of urate stones in an acid urine, patient must also report such unusual symptoms as anorexia, dyspepsia, nausea, loss of weight, pruritus, or jaundice, and upon the appearance of any of these symptoms he must stop taking the drug at once and report for special therapy (carbohydrates intravenously, high carbohydrate diet, vitamin supplements, and so on). Bartels (1943) felt it important to perform liver function tests at intervals during treatment with cinchophen and to stop the use of the drug when the result of the test fell below normal. McCracken *et al.* (1946) think it well to test the urine for urobilinogen frequently. Rawls (1942) reported that the administration of synthetic vitamin K (menadione) appears to lessen the toxic effects of cinchophen on the liver.

A number of years ago Graham reported a patient who had been on a cinchophen regimen without any special protective measures continuously for a period of six and a half years, and doubtless there are many unrecorded instances in which the medication has been continued for an even longer time. It is possible that the occasional reactions to the drug are upon an allergic basis, *i.e.*, acute yellow atrophy being comparable in these cases to the acute agranulocytosis sometimes caused by amidopyrine and other agents. A mild reaction, omitted (but certainly inadvertently) from Hench's list of warning signs, is urticaria (hives), many men feel that when a patient develops an urticarial reaction to the ingestion of a drug he should never again be allowed to take a dose of that drug.

The Salicylates.—Bauer and Klemperer (1944) felt they had demonstrated clearly that results equal to those ascribed to cinchophen can be obtained by the use of salicylates in high dosage and without any inherent risk. Hench [illegible]

Miscellaneous Drugs.—It is not proved, indeed not even strongly [illegible] by results attained, that the routine use of iodides or alkalis or thiamine or live baker's yeast is helpful in the treatment of chronic gout. Long ago it was proved that lithiu [illegible] is indicated if the patient is on a pu [illegible] excessive amount of alkali, the l [illegible] in a dose of 15 to 30 minims (1 to 2 cc.) after each meal. However, if the patient is taking cinchophen or a salicylate and accompanying it with an alkali, the use of acids would of course be absurd.

The Allergic Approach.—Allergists are beginning to interest themselves in gout, and I think it high time There is nothing as yet to report except that of course they are concerning themselves with the possible allergens in the pa- [illegible] its purine content It seems to me that any physician [illegible]

defective low lumbar intervertebral disks though I do not have a clear idea what they do about the matter. Removal to a warm sunny climate is often very helpful. Traeger shrewdly remarked that perhaps most of the "arthritis" cases cured by a trip to Florida or Arizona are in truth only cases of fibrositis.

Reiter's Syndrome

In 1916, Reiter in Germany, and independently Fiessinger and Leroy in France, described cases presenting the symptom triad of non-gonorrheal urethritis, conjunctivitis and arthritis. Reiter thought his case was caused by a spirochete and the French observers considered the dysentery bacillus in the

be. Hollander (1946), whose fifty-three cases seen at a rheumatic disease center in one of the United States General Hospitals during War II is the largest single series I have seen reported, describes the principal characteristics of this syndrome as follows: (a) acute nonspecific urethritis, often without history of sexual exposure and sometimes accompanied by mild transient diarrhea, clearing spontaneously in three or four weeks regardless of treatment

marked; (e) superficial ulcerations on the glans penis, beginning about one month after onset of the disease, and also in some cases keratodermic lesions on the feet and legs, the latter usually clearing in two months but the balanitis possibly recurring independently of the existence of urethral discharge; (f) a sedimentation rate that is most rapid about six weeks after onset of the disease and only gradually returns to normal during three months; (g) roentgenograms of the involved joints usually showing osteoporosis of the approximating bone ends during the second or third month, periosteal proliferation near

occurred between two and sixteen days after the appearance of the urethral discharge and arthritis one to six days later. In one case, however, arthralgic pains in several joints were observed two days before the onset of conjunctivitis and definite articular involvement did not occur until four days later. Sargent's (1945) experience in three severe cases indicated that the syndrome may go considerably beyond the simple triad of urethritis, conjunctivitis and arthritis, for the arthritis may become deforming, the conjunctivitis may involve the cornea and anterior eye chamber, and the urethritis may extend to the bladder and cause urinary symptoms and findings of very substantial

the pain. Some American writers like to include pleurodynia as simply a primary
do so; I
form of t
here.

Psychoneurosis as it affects the locomotor system, perhaps not too well delineated as "psychogenic rheumatism," caused considerable difficulty in differential diagnosis during War II *according to Hench and Boland (1946)*, but they stated that in general primary fibrositis puts its victims at the mercy *of changes* in external environment such as weather, heat, cold, humidity, rest, exercise, etc., whereas the victims of psychogenic rheumatism are more affected by alterations in internal environment such as change in mood or psyche, pleasure, excitement, mental distraction, worry or fatigue.

THERAPY

Prognosis is good in fibrositis in the sense that crippling and deformity are *not to be feared, but it is common experience that to relieve a patient in an*
siege, is easier to desire than
this entity its therapy *is*
ect launch into discussions
of the necessity to eliminate foci of infection, the value of vaccines, histamine iontophoresis, vitamin stuffing (the latest is vitamin E, used in high dosage by
in short,
passé
d, but
the two remedies that seem to be of greatest value are the old ones
heat see the article on Rheuma-
ugh massage should
sed until it becomes

that stretching exercises always should follow massage. Copeman and
man (1947) definitely approve of heat, massage and active muscular movement, and they refer to the success with which the pain may be relieved by local injection of an anesthetic as "well-known"; but they remark that the *trigger-point or the fibrositic nodule is not always an easy target to hit*. Their modification of usual technic consists in anesthetizing the skin over the site of the trigger-point, transfixing the nodule *with a stout, rigid* "record" needle, injecting 10 to 20 cc. of 1 per cent solution of procaine hydrochloride under the
and then sweeping around *the cutting* point of the
the
the
n of
aine
and
solution intramuscularly in patients suffering
small

ests and emotional reactions and
torticollis had begun were determined in so far as possible and the attempt was

advises the early beginning of physical therapy and exercises for the involved joints in order to prevent deformities that will slow convalescence, and finds that hot baths, baking and massage greatly hasten recovery and prevent residual disability. He feels that symptomatic therapy for the eye and skin lesions are perhaps helpful, as are bland urethral irrigations and hot sitz baths for the genito-urinary involvements, but he believes that vigorous therapy may be harmful through prolonging the natural self-limited course of the malady In some of Hollander's cases the course of fever therapy by intravenous typhoid vaccine injections seemed to hasten recovery. He felt that gold was too potentially toxic to justify its use in this self-limited condition.

RICKETTSIAL INFECTIONS

(Epidemic Typhus, Endemic Typhus, Rocky Mountain Spotted Fever, Boutonneuse Fever, Tsutsugamushi Fever, Trench Fever, Q Fever, Bullis Fever, Rickettsialpox, North Queensland Tick Typhus)

The rickettsial organisms, so named by da Rocha-Lima in 1916 in honor of the young American bacteriologist, Howard Ricketts, who had probably first observed them and who himself died of typhus fever, remain a puzzling group having some of the characteristics and attributes of both bacteria and viruses But in recent years sufficient information has been accumulated [illegible]

[illegible]

The essential pathology in the rickettsioses consists in necrotizing damage to blood vessels in various regions of the body, the rickettsiae in some instances [illegible]

often other manifestations of central nervous system involvement; (b) the appearance of a rash some time within the first few days; (c) relatively few complications; (d) death or termination by crisis with few sequelae An additional interesting feature characterizing some of these infections is the fact that the serums of patients agglutinate the OX strains of *Proteus vulgaris*, a positive agglutination of this sort being known as the Weil-Felix reaction

Classification of these diseases is still somewhat confused (Blumer, 1941, said that more than ninety names have been applied to classical typhus alone), but I think the group can be presented with sufficient clarity under the following heads: epidemic typhus, endemic typhus, Rocky Mountain spotted fever, tsutsugamushi fever or scrub typhus, boutonneuse fever, trench fever, Q fever, Bullis fever, rickettsialpox and North Queensland

proportions. He observed ulcers similar to those of the genitals on the inner lips and buccal mucosa. In Vallee's (1946) case not only conjunctivitis but also *keratitis, iritis and iridocyclitis occurred. Twiss and Douglas (1946)* reported that in their two cases, followed for about six months, arthritic changes persisted and they felt it probable that these patients now have a chronic arthritis indistinguishable from other types. Feiring (1946) reported a case in which transient auriculo-ventricular conduction defects indicated that the disease had apparently involved the myocardium. Spontaneous termination of the attack in four to six months does not always erase the picture for relapses occur not unusually; Vallee's (1946) patient had recurrences over the course of sixteen years.

Reiter's syndrome seems to occur exclusively in men and principally in young men, the single reported case in a woman having been so atypical as to raise considerable doubt that it belongs in this category. Vallee (1946) considers that Reiter's major contribution was that he conceived of the syndrome as a new entity not ascribable either to shigellosis or to gonorrhea. *Upon the other hand, Young and McEwen (1946), Kay (1946),* and Wood (1946) feel inclined to believe that the disease is not a separate etiologic entity but simply a combination of the complications of shigellosis (bacillary dysentery). But Harkness (1947) will not accept this. He says that the [illegible] of the other [illegible] "dysenteric arthritis," or Reiter's disease if one wishes, and that the cases now denominated Reiter's disease be described as "non-gonococcal polyarthritis" or simply "the non-gonococcal syndrome." He believes all of these cases to be venereal in origin. Vallee (1946) would also effect a clear distinction between the diarrheal and the non-diarrheal cases and feels that in the latter the genital tract is probably the channel of invasion; the fact that the syndrome has never been reported in women does not eliminate this possibility in his opinion since it is well known that the female genital tract harbors potentially pathogenic agents that either do not cause disease in the carrier or cause at most a leukorrhea that is often overlooked or ignored. In this connection he cites the fact that an earlier writer described the case of a patient whose urethritis and arthritis developed one week following intercourse with a girl whose relations with another man resulted in a non-specific urethritis without arthritis, the girl being known to have a vaginal discharge repeatedly *found negative for gonococci.*

THERAPY

In Sargent's (1945) three cases practically every therapeutic measure [illegible]

improvement after the first two weeks he did not feel that the [illegible] due to any of the treatments employed. About the only positive recommenda- [illegible] (1946) finds [illegible] ed bed [illegible] ditions,

days and mortality is lowest in children and highest in the aged. An oft-repeated adage, well characterized by Dyer (1941) as "rather tiresome but too truthful" is that the extent of typhus at any given time is a current measure of human wretchedness. Close quarters, malnutrition and cold invite it surely.

or louse-to-man transmission of this disease. Zinsser and his associates were of opinion that these cases are recrudescences of European typhus fever acquired at an earlier time in an endemic Continental focus, an opinion supported by the findings of Plotz (1943) with the new complement-fixation test and by the observation by Mooser (1946) of a case of classical louse-borne typhus in Zurich in a man who had suffered from typhus in Russia in 1918. It is definitely a mistake to refer to cases of the endemic typhus of our southern states (see

times there are aching pains throughout the body also The rise in temperature is accompanied by a proportional increase in pulse rate and in the severity of

is very great. On the fourth to seventh day, a maculopapular rash appears which changes from pink to red, then purplish-brown, it involves usually all of the body but is often very sparse or absent on the face and neck. On reaching

nervous system involvement, such as tinnitus, vertigo and deafness. There is usually a loose cough almost from the beginning. Small areas of spontaneous necrosis of the skin are not rare. Yeomans *et al.* (1945) found azotemia (nitrogen retention) present in 52 per cent of their seventy-eight patients with a striking correlation between clinical severity and the height of the nitrogen retention. With one exception, positive evidence of glomerular nephritis was lacking in all cases in which the urine was frequently examined, and follow-up examinations over a period of months showed impairment of renal function only in the rare instances in which it was considered possible that renal disease had existed before the onset of typhus. These observers took azotemia to reflect excessive destruction of body protein, reduced output of urine in the presence of normal kidney function, and sudden and rapid fall in blood pressure associated with evidences of renal insufficiency in severe cases. In addition to vascular and other lesions characteristic of rickettsial infection, Golden's

tick typhus. The therapy and prophylaxis of all these entities may be satisfactorily considered simultaneously.

EPIDEMIC (CLASSICAL OR "EUROPEAN") TYPHUS FEVER

named for one of da Rocha-Lima's co-workers who, like Ricketts, died of the

vast major-

e rubbing of

lation of in-

fected air-borne material may sometimes give rise to the infection. This form of typhus is in the main a disease of the cooler portions of the earth, but at the present time its definite endemic foci are known to be, according to Dyer

zone have had severe visitations of this disease. The typhus years in the United States were 1812, 1830, 1847, 1865, 1881, and 1893; these outbreaks were usually confined to recently arrived immigrants in the seaboard cities, and very probably were more importations of the disease; Canada had a visitation of this sort in 1847, in which year the death toll among immigrants was over 20,000. All wars, with the exception of our Civil War, have felt the severe ravages of typhus; probably the greatest havoc, prior to the twentieth century, was wrought during the Thirty Years' War in the seventeenth century, and next during the Napoleonic campaigns. In War I the Allied armies on the western front were practically typhus-free only because the Germans and Austrians were fiercely fighting to keep it away from their front lines, their rear being heavily attacked by it from Russia Eastern Europe and the Balkans suffered severely during and after the War; the number of persons known to have perished in Rumania was nearly one million and estimates place the number at several millions in Russia. The incidence of the disease in Russia and its dominated states during the current post-War II period has not yet been made known Sadusk (1945) says there occurred less than fifty cases of this type of typhus in our entire Armed Forces, only twenty-one cases occurred after the crossing of the Rhine, according to Middleton (1947), though the

had enteritis, 10,000 had tuberculosis, and 5000 had famine edema.

no epidemic has ever been more widely publicized than that which occurred

reported a mortality of 18.5 per cent in 9404 cases recorded in

and 20.2 per cent when the epidemic reached its height, with 40,084 cases, in 1943. The incubation period seems to be from five to as much as twenty-two

days and mortality is lowest in children and highest in the aged An oft-

or louse-to-man transmission of this disease. Zinsser and his associates were of

observation by Mooser (1916) of a case of classical louse-borne typhus in Zurich in a man who had suffered from typhus in Russia in 1918. It is definitely a mistake to refer to cases of the endemic typhus of our southern states (see

temperature accompanied by nausea and vomiting and a headache; sometimes there are aching pains throughout the body also The rise in temperature is accompanied by a proportional increase in pulse rate and in the severity of the headache, but the gastro-intestinal symptoms disappear early. The temperature often reaches 105° F (40 5° C.) on the second or third day, to remain with remarkably little daily remission until the close of the attack. Prostration is very great. On the fourth to seventh day, a maculopapular rash appears which changes from pink to red, then purplish-brown, it involves usually all of the body but is often very sparse or absent on the face and neck. On reaching full efflorescence, some of the spots become hemorrhagic and purpura appears irregularly. The patient experiences sleeplessness from the beginning, which

nervous system involvement, such as tinnitus, vertigo and deafness. There is usually a loose cough almost from the beginning. Small areas of spontaneous necrosis of the skin are not rare. Yeomans *et al* (1945) found azotemia (nitrogen retention) present in 52 per cent of their seventy-eight patients with a striking correlation between clinical severity and the height of the nitrogen retention With one exception, positive evidence of glomerular nephritis was lacking in all cases in which the urine was frequently examined, and follow-up examinations over a period of months showed impairment of renal function only in the rare instances in which it was considered possible that renal disease had existed before the onset of typhus. These observers took azotemia to reflect excessive destruction of body protein, reduced output of urine in the presence of normal kidney function, and sudden and rapid fall in blood pressure associated with evidences of renal insufficiency in severe cases. In addition to vascular and other lesions characteristic of rickettsial infection, Golden's

though the discoloration following the rash usually fades gradually and convalescence may be very protracted. The two complications chiefly to be feared are secondary bronchopneumonia and thrombosis of the large vessels. Aschenbrenner and Marx (1943) observed an unexplained rise of temperature about the first week of convalescence in forty-six of 691 cases; this fever lasted only one to three days in most instances and was considered of importance only because it was likely to cause needless anxiety. As sequelae in a group of 500 patients Siedek *et al.* (1943) found various disturbances of the central nervous system in 35 per cent and cardiovascular disorders in 45 per cent.

The Weil-Felix agglutination test is not of very great value as an early diagnostic aid in epidemic typhus for the reason that it unfortunately does not become positive until the rash has appeared, and sometimes not even until late in the second week; agglutination with the OX19 strain, which is more reliable than the OX2 strain, will differentiate typhus from tsutsugamushi fever but not from Rocky Mountain spotted fever. Nelson and Cruickshank (1945) were unable to confirm the finding earlier reported by another author that the serum of pregnant women agglutinates *Proteus* OX19 even in the absence of typhus fever. Dyer (1944) said that the complement-fixation test, using typhus rickettsias as antigen, becomes positive during the second week and is of value in differentiating typhus from Rocky Mountain spotted fever. Fitzpatrick's (1945) study indicated that the rickettsial slide agglutination test may also be a useful diagnostic aid.

Endemic (Murine) Typhus Fever

This form of typhus, now recognized to be a disease of considerable importance in the United States, differs radically from the classical form of epidemic typhus (see above) in several respects. In the first place, the great reservoir of the disease is not in man but in the common gray wild rat. In the second place, it is not conveyed by the body louse but the rat louse and the rat flea, particularly the Oriental rat flea, *Xenopsylla cheopis*, which keeps the disease going in rats and occasionally conveys it to man probably in the same manner in which epidemic typhus is conveyed (see above). In the third place, the disease does not occur in man in large epidemics under conditions of privation and want but remains endemic, the cases at most grouping themselves about locations especially heavily infested with rats, such as shops, groceries, grain depots, warehouses, and at times the lowest class of dwellings. And finally, unlike epidemic typhus, which occurs predominantly in the winter, endemic typhus though occurring throughout the year reaches its very definite peak in the late summer months. Most of the patients are young adult males. Stuart and Pullen (1945) pointed out that failure to observe a skin rash on Negro patients may result in a missed diagnosis in many instances and account for the impression that endemic typhus is rare in the Negro, indeed more than half of Miller and Beeson's (1946) 126 patients were of the colored race. Until recently nearly all cases have occurred in small towns and cities, but latterly the incidence has been rising in rural areas, which may be a reflection of the establishment of the disease

Just how long endemic typhus, whose causative organism is *Rickettsia mooseri*, has been prevalent in this country we do not know, but it was first recognized in Georgia by Paullin in 1913 and has been reported with increasing frequency since Maxcy's intensive studies began in 1923. In the ten-year period, 1929–1938, the number of reported cases was 11,427, but Kemp (1939) undoubtedly voiced the consensus in saying that the true number of cases is very likely greater than that reported. Practically all of these cases have occurred in North and South Carolina, Georgia, Florida, Mississippi, Alabama, Louisiana, Texas and southern California, with a few scattered cases in other southern states, most notably Tennessee and Arkansas, and a very few cases indeed elsewhere in the country. This distribution is certainly not that of the common rat, and it may not be purely climatic for there is the flea also to consider *X cheopis* was originally found

likely that as *X cheopis* increases its territorial invasion, endemic typhus will go along with it; indeed, the reports of Topping and Dyer (1943) and of others showed that it is already occurring in several northern states. While much of the investigative work on endemic typhus has been done in the United States, the disease is now known to occur very widely throughout the world, indeed it would seem that this is the most wide-spread of all the rickettsial infections The entity called "tabardillo" in Mexico is apparently at times endemic typhus and at other times louse-borne epidemic typhus.

eight and twelve days with extremes of five to fifteen days The Weil-Felix test is positive with the OX19 strain in endemic as in epidemic typhus, but leukopenia is more often a characteristic of the endemic form of the disease and there has also been developed a helpful murine complement-fixation test. In the age of greatest incidence (young adults) mortality is between 1 and 2 per cent, according to Gordon (1940) it is 5 to 7 per cent in those between forty-five and sixty-five years and about 30 per cent in those above sixty-five

Rocky Mountain Spotted Fever

The geographical connotation of the name of this disease no longer correctly indicates its distribution, *for while ten years ago 70 per cent of the cases* did occur in the Mountain and Pacific States, in 1945 those reported from the Central and Eastern States comprised 87 per cent of the total. This type of spotted fever has now been diagnosed in forty-seven of the forty-eight states, and Ravenel (1947) says that during the past ten years there has been an annual occurrence of 400 to 560 cases with ninety to 137 deaths One may therefore reckon the crude overall mortality rate as between 22 and 25 per cent Formerly it was believed that the eastern variety of the disease

tence of mite-borne typhus could also be assumed in Thailand; these authors further stated that the disease under present consideration occurs not only in North Queensland in Australia but also at scattered points along the eastern coast of that continent to as far south as the city of Sidney in New South Wales. Its existence in the Marshall and Caroline Islands is not yet certain. A great reservoir for the disease apparently exists in numerous rodents and bush and swamp fowl Like Rocky Mountain fever (see above), which it seems to resemble very much clinically, tsutsugamushi is a rural disease, the latter differing from the former chiefly in the following particulars: (a) The causative organism, *Rickettsia orientalis*, (*R nipponica*, *R. akamushi*, *R. tsutsugamushi*) is transmitted by a mite. (b) A necrotizing lesion appears at the site of the bite and there is adenitis of the drainage area and sometimes of other areas as well (the exception here is Malayan and Australian rural typhus, in which this lesion is rarely seen, and it is said not always to occur in Formosa either). (c) The rash seems often to make its appearance first on the trunk, but in many of the dark-skinned natives in the affected regions it is not possible to make out a rash at all. (d) The Weil-Felix reaction with the OXK strain is usually positive after the tenth day but only negative reactions are obtained with OX19 and the OX2 strains; hence differentiation between tsutsugamushi and typhus can be made by employment of the Weil-Felix reaction.

Tsutsugamushi fever came to be a very important entity in the Armed Forces in the Southwest Pacific area during War II. Sapero (1946) reported that 7421 cases had been diagnosed. In an outbreak in New Guinea, Irons and Armstrong (1947) found that the incubation period appeared to be usually between nine and twenty-one days; Mackie (1946), who headed the Typhus Committee sent out to study the matter in the endemic Assam-Burma area, used an arbitrary incubation period of ten days in order to determine the approximate date of infection. Mortality varies widely in reported series of cases between 2 and 40 per cent, indeed according to Simmons *et al.* (1944) mortality may be as high as 60 per cent, but I do not believe that such a high death rate has been reported outside of Japan. In the 200 cases seen by Lipman *et al.* (1944) during War II in New Guinea, the mortality rate was 10 per cent, and Fairley (1945) said that the over-all rate among British troops in the Southwest Pacific was about 8 per cent. Scheie (1946) obtained some diagnostic aid from the fact that engorgement of intraocular veins occurred in 67 per cent of the eyes of 451 patients, edema of the disk and retina in 30 per cent, retinal hemorrhage in 6 6 per cent, exudates in 4 9 per cent, uveitis in 1.3 per cent and vitreous opacities in 4 6 per cent; but Dame (1945) found that the eye symptoms were transient and of minor importance. Minor transient involvement of the ear occurred in 11 per cent of Dame's patients In a severe outbreak involving fifty-one patients with a mortality of 25 per cent, Ripley (1946) found evidence of involvement of the central nervous system in all cases, the manifestations ranging widely from transient toxic cerebral symptoms to evidence of severe wide-spread inflammation resulting in coma and death. However, it has been authoritatively stated from the Office of the Surgeon General (Bull. U.S. Army Med. Dept., 84, 21, 1945) that while convalescence from scrub typhus is often prolonged and many patients may for a time present the picture of neurocirculatory asthenia, recovery from the disease is [illegible] ly complete without any residual damage to [illegible] heart or other [illegible] said it was learned during th[illegible] most [illegible] (1946) [illegible] returned to

full duty in less than nine weeks when a program of directed reconditioning was included in the convalescent period. In reinfections, which are not uncommon, the attack is usually mild. Mackie (1946) feels that, since transovarial transmission occurs in the mite, and a rough parallelism has been shown to exist between the density of the mite and the prevalence of the disease, it is logical to regard the mite both as an important reservoir and a vector—a viewpoint that would have the rodent or bird acting merely as the obvious mechanism for dissemination of the infected mites The disease has also been contracted through accidental laboratory inhalation of infectious material

Trench Fever

Trench fever is a practically nonfatal but extremely debilitating disease caused by *Rickettsia quintana*, the organism being transmitted from man to man by the body louse. Graham, of the British Expeditionary Force, first described trench fever as a new disease in 1915, though it probably existed

to all the fighting fronts in War I by the movement of German and Austrian troops. In 1917, Grieveson stated that at one time 60 per cent of all patients

alone in maintaining that trench fever was continuing its endemic existence in certain parts of Eastern Europe, but time has certainly borne him out for it reappeared in the German Army during War II and outbreaks were described in Poland, Russia, Rumania, Italy, France and Belgium For example, Bernsdorf (1943) said that the problem became a very serious one after February, 1942, but I imagine the situation was got in hand very quickly when the new delousing powders became available Hurst (1942) offered as rather convincing proof of his contention that the British Army had not brought the

of lice-infest

the reappear

form had it been endemic in the country.

After an incubation period of fifteen to twenty-five days, and prodromal symptoms which are not characteristic, the onset is usually sudden, *i e*, all of the symptoms have usually developed in twelve to twenty-four hours from the first appearance of any one of them. There is chilliness or rarely a definite chill, prostration of varying intensity, rise of temperature to 103° F. (39° C) or more, anorexia and sometimes vomiting and sweating, frontal headache and severe pain "behind the eyes," and generalized pain and tenderness in both muscle and bone; the especial severity of this latter symptom in the lower legs, particularly at night, gave the affection its popular name of "shin-bone fever" A macular rash sometimes occurs on chest and abdomen. Held (1944) stated that bodies resembling rheumatic nodules can be found, but I have seen no other mention of this finding. The course of a particular case is not predictable, sometimes there is but one bout of fever which is over in a few days, or the attacks occur regularly at three- to seven-day intervals, or the case runs a protracted typhoid-like course. The bronchitis

present in some cases during War I was not considered to be of serious moment, but we do not know as much as might be desired of the extent of the circulatory involvement during the earlier stages of the attack. Certainly many of the cases of "effort syndrome" of those days were considered to have had their inception in a bout of trench fever, but Hurst (1942), looking back upon his experience, felt that these cases were only to a minor degree a direct result of the toxemia of trench fever and were mainly functional and preventable conditions resulting from too much coddling on the part of over-conscientious medical officers.

According to Dyer (1944) none of the OX strains of *Proteus vulgaris* is agglutinated by serum from patients with trench fever; in other words the Weil-Felix reaction is negative. It was hoped that the Germans and Russians would have something new to tell us about this interesting disease after the close of War II, but so far the accounts have not been forthcoming

Q Fever

This is an interesting "new" entity. In 1937, Derrick reported among abattoir workers and dairy farmers in Queensland, Australia, nine cases of a disease resembling mild typhus but differing from it in the absence of a characteristic rash and the consistently negative Weil-Felix test. Burnet and Freeman showed that the organism, since denominated *Rickettsia burneti*, is the causative agent. It has been established that in Queensland a reservoir of the disease exists in the bandicoot and that a certain tick is the natural vector among these animals. But there are no records of this tick attacking man (though Smith, 1941, stated it will do so readily in the laboratory) and a history of tick bite has not been a feature of the human infections Derrick *et al.* (1942) found cows susceptible to Q fever and also that natural infection occurs among them in the endemic area in Australia An organism, at first called *R. diaporica* but now recognized as identical with *R. burneti*, was isolated from wood ticks in our West in 1938, and in the same year Dyer reported an attack of disease in a laboratory worker who had had some contact with this organism; later this "Nine Mile" fever (so designated from the site in Montana from which the original batch of infected ticks had come) appeared in epidemic form in one of the United States Public Health Service laboratories in Washington, D.C., in a building housing rickettsial studies. Another outbreak in these laboratories, now located in Bethesda, Maryland, was reported in 1946, and one had also occurred during the war in laboratory workers at Fort Bragg. Allied troops were several times attacked by the disease in Italy, Corsica and Greece. No reservoir of infection or arthropod vector was discovered in these Mediterranean outbreaks, though the affected troops for the most part were billeted in situations in which they were in close contact with cattle, rodents and pigeons and with the dust of attics and haylofts. It was therefore assumed, as Derrick had earlier done in Australia, that transmission might have been through the inhalation of the dried infective excreta of arthropods. In the outbreak among stock handlers and slaughter-house workers in Amarillo, Texas, reported by Topping *et al.* (1947), there was an attack rate of 40 per cent among 136 employees of three establishments, fifty-five cases developing with death in two. The epidemiologic investigations of this outbreak revealed that cattle were probably the source of the human infections.

In addition to the absence of the Weil-Felix reaction, Q fever is unique

among the rickettsial infections in that no rash occurs and there is no leukocytosis and, as pointed out by Cheney and Geib (1946), the rickettsiae are found extracellularly as well as intracellularly following animal inoculation. Irons and Hooper (1947), reporting on the Amarillo outbreak, listed the [illegible]

to the respiratory tract, and comparatively rapid convalescence In cases seen among troops returned to this country from Italy, the average period of illness was only four days and fewer than one in ten had an illness lasting longer than a week In the Amarillo cases primary atypical virus pneumonia was excluded because of the acute onset, lack of symptoms referable to the upper respiratory tract, comparatively rapid convalescence, and lack of cold agglutinins in convalescent serums Lack of history of contact with birds seemed to rule out the probability of psittacosis. Irons *et al.* (1947) found the complement-fixation titers low as a rule during the first week of illness but subsequently generally reaching and remaining at high levels at least for a few weeks Therefore the complement-fixation test was of great assistance in retrospective diagnosis in the Amarillo cases. In the Mediterranean cases the incubation period seemed to have been from fourteen to twenty-six days

Bullis Fever

[illegible]

committee of investigation, had thoroughly examined such patients as remained in the hospital and had studied the clinical records of those who had been returned to duty and agreed that the entity was at least a definite one. The onset in most of these cases was abrupt with initial chill or chilliness and a temperature that rose quickly to 102° to 105° F. (38 9° to 40.5° C.). A few of the patients gave a history of prodromal symptoms for a few days prior to the onset and during the attack most of the men complained of severe postorbital and occipital headache; pronounced lassitude, prostration, anorexia and general weakness were noted during the febrile stages of the disease and a few patients were nauseated and vomited. After an average febrile course of five days, with extremes of four to fourteen days, the temperature subsided by lysis In some of the severe cases a rash sometimes resembling that of German measles and at other times that of typhus appeared but remained only about forty-eight hours. Considerable weight loss was noted in many of the patients and convalescence was protracted in the cases in which the illness had been severe. Respiratory tract involvement did not occur though the throat was usually slightly red, but all of the patients had enlargement of at least one set of lymph glands and commonly general lymphadenopathy, the glands were in many instances acutely tender and their involvement persisted throughout the acute stage of illness but disappeared rather promptly with the clearing of the other symptoms. A constant laboratory finding was a very pronounced leukopenia occurring on the second or third day and associated with neutropenia; in many instances the

leukocyte count was said to have dropped to 3000 or below and one patient had a polymorphonuclear count of only 23 per cent. Weil-Felix tests using OX19, OX2 and OXK antigens were consistently negative, as were indeed the results of the numerous other laboratory studies that were performed. It was thought that the incubation period of the disease was seven to ten days

Pollard *et al.* (1946) have been able to isolate the rickettsia causing this new disease from tick emulsions from Camp Bullis, have propagated it in the yolk sac of developing chick embryos, and after such propagation for twelve generations have reproduced the disease in the human; they have also reproduced the disease in the human by inoculation of blood from febrile cases of the disease. The investigations of Bader and Anigstein (1944), Pollard *et al.* (1946) and Livesay *et al.* (1946) have failed to reveal any im-

RICKETTSIALPOX

During the summer of 1946 a peculiar febrile disease appeared in New York City. A total of 144 cases was reported, most of the patients being residents of a new housing development, but Greenberg *et al.* (1947) said that additional cases had been brought to their attention by physicians in the city who had

where on the body, the lesion beginning as a more or less round and firm red papule which then developed a deep-seated firm vesicle in its center and ultimately shrank and dried and formed a black eschar. The surrounding skin was erythematous but not indurated and the lesion was neither tender nor did it itch. The regional lymph glands were usually enlarged and sometimes slightly tender but lymphangitis was not noted. Then after five to ten days the systemic symptoms appeared abruptly with chills, remittent fever, sweating, lassitude, headache, backache and general muscular soreness. *Photophobia*, less severe than that seen in measles, was not an infrequent symptom. At the time of the appearance of the fever, or three or four or even six days later, a maculopapular rash appeared over the body with deep-seated vesicles that often dried down to form black crusts which ultimately fell off without scar formation. There was no pattern in the distribution of the rash except that it did not occur on the palms and soles and was in a few instances seen in the mouth and on the tongue. The patients felt quite ill but did not appear particularly toxic. There was moderate leukopenia in twenty-one of the twenty-two cases ... other laboratory evidences of diagnos-

n a week

therapy

was found to be of value.

Because of the peculiar appearance of the lesions and the fact that the outbreak strongly suggested some sort of rickettsial infection, the syndrome was given the name "rickettsialpox." Huebner *et al.* (1946), of the U.S.P.H.S., undertook a very thorough study of this new entity, with the following results (a) an organism was recovered from the tissues of a mouse inoculated with blood drawn from a patient on the second day of fever, and from a yolk-sac culture of this organism antigens were prepared that were shown to fix com-

plement with serums drawn from convalescent cases; (b) this agent, to which the name *Rickettsia akari* has been given, was isolated from the house mites collected in the house of a patient and also from a mouse bitten by one of these mites So it would seem that in rickettsialpox we have a new American urban rickettsial disease transmitted by blood-sucking mites with its animal reservoir possibly in the house mouse.

North Queensland Tick Typhus

In 1946 Andrew et al. reported twelve cases of an ...

to have been bitten by the most abundant of the four tick species infesting the region, and in several of them eschars developed at the site of the bites as in scrub typhus It seemed likely that seven to ten days was the incubation period. The disease ran a course rather similar to that of boutonneuse fever

titer and a negative OX2, though in some instances OX2 was higher than OX19; in all cases OXK ... Plotz et al. (1946) ... recovered from one of ... epidemic typhus, ende... neuse fever, South Afr... cluded that the causative agent is one that had not been described before. Hence this disease must be at least tentatively recognized as a separate type of rickettsial infection

THERAPY OF THE RICKETTSIAL INFECTIONS

Symptomatic, Dietetic and Nursing Care.—All experienced observers ...

treating this disease, gave vitamins in large quantities and vitamin K parenterally to all who were jaundiced and to a number of others who showed hemorrhagic tendencies and a somewhat low prothrombin activity. Ravenel (1947) also favors the administration of vitamins by mouth, by gavage or by the parenteral route if necessary in Rocky Mountain spotted fever—thiamine to help prevent shock, ascorbic acid to obviate endothelial damage to blood vessels, vitamins B complex and K for damage to the liver and for increased prothrombin time. The mouth must be kept clean else it becomes very foul and an easy prey to secondary infection; liquor antisepticus of the N.F. is a good preparation to use for the purpose. For treatment of the cough see the article on Common Cold. All authorities agree that it is usually necessary and advisable to control the insomnia of fulminating attacks by the use of morphine. If this drug is not being used some less powerful analgesic will be indicated to combat the headache: phenacetin (acetphenetidin) in a dose of 5 grains (0.32 gm.), or acetanilid, 3 grains (0.2 gm.); either of these may be *reinforced by the addition of ½ to 1 grain (30–60 mg) of codeine sulfate* and one of the barbiturates, such as phenobarbital, ½ grain (30 mg). In many instances of "malignant" restlessness in scrub typhus, Sayen *et al.* (1946) found the barbiturates ineffective and obtained best results with one ounce (30 cc.) of paraldehyde in oil by rectum, repeating the dose every few hours; they felt that this measure was sometimes lifesaving. Tattersall (1945) found lumbar

cerebral symptoms in scrub

as the skin is very prone to ulcerate and become gangrenous in these affections

conditioning of wards was very helpful in the

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improved; indeed they felt that air conditioning was a measure that might turn the tide in a favorable direction for dangerously ill patients

Shock Therapy.—Lipman *et al* (1944) sometimes gave whole blood transfusions when anemia was present in tsutsugamushi fever and blood plasma

was routinely used in

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cated in about one-fourth of the cases,
intestinal hemorrhage, abnormalities of
illness with a relatively marked drop ir
Tierney and Yeomans (1946) looked upon a marked drop in urine output,
particularly if associated as an ominous
sign urgently requiring t nel
(1947) says that in Rocky vel

vascular damage and hepatic

of plasma or

intained by

further injections of plasma and by a high protein diet, blood transfusions being freely given if anemia develops. So it seems that the earlier fear of transfusions, engendered by the vascular lesions, has been dispelled by a larger experience

Para-Aminobenzoic Acid.—This agent, known for some time to be effective in experimental rickettsioses in the laboratory, has now been shown to be of

considerable value in all of the more severe of the rickettsial diseases in man. The action is apparently not a direct chemotherapeutic one on the rickettsiae themselves but rather an interference with their proliferation within tissue cells as a result of metabolic stimulation of these cells through modification of some enzyme system. In their study of twenty treated and forty-four untreated cases of epidemic typhus, Yeomans *et al.* (1944) felt that when treatment with para-aminobenzoic acid was started in the first week of illness the clinical course of the disease was rendered much less severe and its duration was con-

be determined. In the untreated group, twenty-two of the twenty-nine had fever for twelve or more days whereas in the treated group only seven of twenty-nine had a fever for so long. There was one fatality in each group. Tierney (1947) treated eighteen patients with tsutsugamushi fever, employing sixteen alternate untreated cases as controls. There were ten more days of fever in the average of the control cases than in the average of the treated

notable that all who observed the patients felt that the disease process had certainly been altered by the agent. The incidence of complications was definitely less in the treated cases, and the majority of the patients who received para-aminobenzoic acid required a much shorter period of convalescence than the control cases. No deaths occurred among the treated patients but three died in the untreated control group. The largest series of cases of Rocky Mountain spotted fever treated with para-aminobenzoic acid that has come to my attention is that of Flinn *et al.* (1946), there were no untreated controls, but it was felt that there was very definite clinical improvement in most of the ten treated patients, the course being much milder than that characteristic for

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output in the attempt to keep the concentration of para-aminobenzoic acid in the blood between 10 and 20 mg. per cent, and therapy continuing until the patient's temperature was normal for twenty-four hours. But Ravenel (1947) says that in the light of present knowledge both the dosage and the concentration of para-aminobenzoic acid in the blood in these cases of Yeomans *et al.* were probably too low. To his own five patients with Rocky Moun-

occurred; after the febrile period was over he often reduced the blood level to 10 to 20 mg. per cent without relapses occurring, the use of the drug being continued one week after the temperature had returned to normal. The chief signs of the overaction of para-aminobenzoic acid are acidosis, leukopenia, abdominal distention, and delirium.

Antiserum.—Topping (1943) produced an immune serum in rabbits for employment in Rocky Mountain fever cases. In a group of fifty-two patients treated with this serum there were only two deaths, both in males sixty-six and seventy-two years of age, respectively, or a fatality rate of 3.8 per cent as compared to the expected rate of approximately 18.8 per cent. Topping felt that these results were not conclusive mainly because of the relatively sma" number of cases in the series but that they warranted further employment o this serum. Harrell *et al.* (1944) felt that Topping's serum was effective only in the first three days of the rash in Rocky Mountain fever because after that time the intranuclear location of the rickettsiae would oblige any therapeutic agent to pass through two cell membranes in order to reach them. Yeomans *et al.* (1945) used hyperimmune rabbit serum in twenty-five cases of epidemic typhus in Cairo under conditions in which it was not possible to use alternate cases as controls. They felt that the effect of the serum was closely related to the duration of illness at the time it was given, the results with ten patients treated on the second and third day of the disease being almost uniformly good whereas when therapy was begun on the fourth, fifth and sixth days it was more difficult to be certain that the course of the disease had been influenced. The use of immune horse serum in epidemic typhus was reported in 1941 by Durand and Balozet, and again in 1944 by Wolman, the latter's findings being practically the same as those of the earlier workers. There was no significant difference in the length of the illness in the 220 treated patients as compared with that in the 220 untreated controls; the death rate in the treated patients was 3.6 as compared with 10.9 per cent in the controls, and of the seventy-one patients who received serum before the seventh day of illness none died. This study of Wolman's was a very laudable one since the serum was given to alternate cases in a large group of patients, but it would have been made additionally interesting had he analyzed it from the standpoint of the age groups of his patients since the mortality in typhus is closely related to age. It seems extremely doubtful that antiserum will hold its own against para-aminobenzoic acid.

Convalescent Serum.—Convalescent serum seems not to be of proved value in any of the rickettsial infections though it has been tried in practically all of them.

Miscellaneous Agents.—Neither the *sulfonamides* nor *penicillin* has been found of value in any of the rickettsial diseases. *Quinacrine (atabrine)*, introduced into rickettsial therapy by the Germans who were combating epidemic typhus in their armies during War II, has not proved really useful. The intravenous administration of *neoarsphenamine in aqueous metaphen solution* in Rocky Mountain fever was the subject of a brief favorable report several years ago, but since nothing further has been heard of this it has probably been found unsatisfactory upon more extensive trial. During War I the Germans reported *collargol* to be of specific value in the treatment of trench fever. Sweet and Wilmer (1919) also employed this agent with good results in thirty-five cases in the British Army, but they were hesitant to ascribe all the credit to this therapy in a disease so variable in its course as trench

fever According to Arneth (1942), collargol was being used again by the Germans in War II; a pronounced febrile reaction follows its injection, and

also in Germany during War II, claimed that in epidemic typhus he had saved a number of lives by injecting *insulin* to the point of causing hypoglycemia, then following with dextrose by mouth or intravenously. Schmidt's paper, however, was a very unsatisfactory one from which to draw conclusions. The peculiar form of therapy known as "*spinal pumping*" (described in Acute Rheumatic Fever) has been employed in epidemic typhus by the Russians, Yarygin and Nagibina (1944), with allegedly good results, the patients being given large dosage of salicylates on the day before and the day following the pumping. The use of *digitalis* in the usual manner in patients beginning to show signs of heart failure is recommended by most writers, but Ahlm and Lipshutz (1944), describing a considerable experience in tsutsugamushi fever, stated that in these cases digitalis has no effect on the rate or the rhythm of the heart nor does it affect the outcome in any way. The study of Woodward and Bland (1944) reemphasized the fact that in epidemic typhus the circulatory collapse is primarily of peripheral origin; they did not find digitalis indicated in any of their thirty very thoroughly studied cases.

PROPHYLAXIS OF THE RICKETTSIAL INFECTIONS

Protection against Lice and Mites.—Since the vector of epidemic typhus and of trench fever is the human louse, and the vector of tsutsugamushi fever and probably rickettsialpox is a mite, a most important prophylactic measure

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Louse and Mite infestations in Index) Of course in tsutsugamushi fever it was also of great importance to effect clearings about all dwellings and to attempt to exterminate the rodents, notably rats, that harbored the mites. Sleeping on raised floors was also found to be very helpful in the endemic areas However, these latter are matters that are not strictly medical and therefore space cannot be given to a description of them in a book of this limited scope.

Georgia· (a) educational meetings designed to acquaint the people with the nature of the transmission of the disease; (b) removal of rat harborage such as trash, rubbish and old lumber piles, and insistence upon the use of

Wiley (1946) has written that the results of rat poisoning activities utilizing the new rodenticides 1080 and, to a limited extent, ANTU, have been so

successful that the average time necessary to free rat-proofed buildings of rats has been greatly reduced; also that the application of DDT dust to rat-runs has demonstrated that excellent rat-flea control can be obtained for periods up to three months.

Protection against Ticks.—This is important in Rocky Mountain spotted, Bullis, boutonneuse and Q fevers and in North Queensland tick typhus. Of course, as Parker (1938) well said, the best method of avoiding infection is to stay away from regions known to be heavily tick-infested, but for a large part of the population this is impossible. Dogs should be frequently deticked; keeping them clipped during the summer will facilitate this, and dusting frequently with flea powder is also helpful. Children associating with dogs or resident in the country, or even playing on vacant brush-grown lots in the city, should have their heads, necks and bodies examined several times daily. The important thing is to get the tick off at once. Remove him with forceps or while wearing gloves because crushing him in the fingers is dangerous. Sometimes in pulling him away the mouth parts remain in the wound site, which is undesirable, therefore some men advise forcing the tick to detach himself by applying ether, benzine, turpentine, or tobacco juice to him. Wilson (1940) described the following simple method of accomplishing the same thing: strike an ordinary household match, shake it out as soon as it flares, and apply the hot head to the rear end of the tick; he will quickly withdraw his beak. Do not apply the flaming match for this will kill the tick before he can withdraw. Apply tincture of iodine to the wound site, preferably boring in a toothpick end saturated with it, or apply a silver nitrate stick.

When tick-infested areas must be visited by men necessarily engaged in outdoor work or by campers, hunters, etc , the following precautions (con-

the neck to feel for ticks that may have reached that first area of expo- skin. (c) The entire body and the inside of the clothing should be thoroughly examined at least twice daily. (d) Upon retiring remove all clothing and place it far enough away that ticks cannot crawl from it to the bed. (e) Ticks tend to gather in the brush along old trails, in sagebrush and in the grassy strips in the middle of little used roads.

Protective Vaccines.—In *Rocky Mountain spotted fever* two vaccines are now available. The first of these, the so-called Spencer-Parker vaccine, is prepared from infected tick tissues treated with phenol and solution of formaldehyde and is dispensed from the United States Public Health Service Laboratory at Hamilton, Montana, and the National Institute of Health, Bethesda, Maryland. Usual dosage is 2 injections of 2 cc. each, given five days apart and repeated each year in individuals resident in endemic areas, though in some areas of exceptionally high case fatality 3 injections have been used. Parker (1941), summarizing the experience of fifteen years with this vaccine, was able to show very definitely that persons vaccinated the same year they become infected with highly virulent strains are sufficiently protected to lessen greatly the severity of the disease and to insure recovery;

against less virulent strains full protection apparently sometimes occurs. The greater number of years a person has been vaccinated the greater his protection, children being in any case more protected than adults, it seems. Insufficient data are available upon which to form an opinion of the protective value of this vaccine in the Eastern form of the disease. The second type of vaccine is that prepared from the infected yolk sacs of fertile hens' eggs by the method of Cox, it is commercially available, but unfortunately I am not able to state precisely how effective it has been found to be.

In *epidemic typhus*, of which man is the sole animal reservoir, much might have been expected from vaccines but it was not until very recently that a sufficiently innocuous preparation became available for mass immunization. Now, as a result of the yolk sac method employed by Cox, we have satisfactory methods of immunizing with killed rickettsiae During War II, typhus vaccination was required for all military personnel having opportunity to come in contact with the disease It was administered in dosage of 1 cc at intervals of seven to ten days for three injections, a "booster" dose of 1 cc. being thereafter

require special laboratory studies for their diagnosis However, Ecke *et al.* (1945), of the United States Typhus Commission, were able to compare the course of the disease in fifty-four unvaccinated patients in Cairo with the course in sixty-one patients who had received, previous to the onset of illness, one or more injections of Cox-type vaccine They concluded that two or more doses of vaccine given three weeks or more before the onset of typhus reduce the mortality as well as the severity of the naturally acquired disease But Gilliam

Beattie's own verdict on his results with regard to the efficacy of the vaccine was "not proven" Perhaps, however, one should also mention the use of the vaccine by Berke (1946) in Afghanistan, who reported that three inoculations of 3122 persons yielded a notable degree of protection in that only mild cases were recorded with no deaths, while the cases were more serious and deaths

zation, the second group allergic reactions caused by some residual egg allergen in the vaccine. The same precautions as those taken before injecting horse serum products should be taken before injecting this vaccine in order to avoid serious and possibly fatal reactions in egg-sensitive individuals.

At present vaccines are not available against *trench, boutonneuse, Q,* or *Bullis fevers,* or against *endemic typhus* or *North Queensland tick typhus.* Plotz and Wertman (1945) showed that the previous administration of epidemic typhus vaccine does not affect the course or severity of endemic typhus It does not seem that there is as yet available a report on the efficacy of the *tsutusgamushi fever* vaccine with which large numbers of Allied troops were immunized after the close of War II

SANDFLY FEVER

(Three-day Fever, Pappataci Fever)

This disease, caused by a filtrable virus conveyed by the night-biting sandfly, *Phlebotomus papatasi,* has a very wide distribution in tropical and subtropical regions. It has been reported throughout the Mediterranean basin and the Near East, in Eastern and Central Africa, in parts of southern Russia, India, Burma and China, and it has been claimed to occur, according to the Bulletin of the U. S. Army Medical Department (80, 15, 1944), in southern Japan, the Ryukyu Islands, in northern Argentina and in other parts of South America. In the Pacific island areas, Phlebotomus has been reported from [illegible] Mumford [illegible] of [illegible] he disease is not known to occur in the United States. In the indigenous regions [illegible] large proportion [illegible]

extreme rarity, but an attack may nevertheless incapacitate the patient [illegible] than an attack of vivax malaria The bout is usually characterized by abrupt onset with a fairly high fever, backache, severe joint and muscle pains, stiff [illegible] the eyes and on movement of the eyes, sometimes [illegible] junctival [illegible]

Markedly inflamed papules usually appear at the sites of the bites [illegible] or two after they have been received and persist for four or five days. According to Sabin *et al* (1944), who made an extensive study of the disease during War II both in the field and in experimental infections in volunteers, the blood pressure is sometimes low and the pulse rate slow during an attack; these [illegible] also established the fact that although there may or may not be a [illegible] relative

'e serum tested for its ability to blanch a definite scarlet rash on another

'ever is established, and if they do not the patient does not have scarlet

1689) has left a first-hand account, separating it from measles and giving it its present name, *its confusion with measles, however, persisted for a* long time after his day. Following the period corresponding roughly with the American War for Independence in the late eighteenth century, scarlet fever spread rapidly over both hemispheres and now occurs all over the world but is extremely rare among natives of Africa and India.

THERAPY

Nursing Care and Diet.—Mild cases of scarlet fever require practically no treatment, though the physician and nurse will often be greatly taxed to keep the child in bed until the danger of delayed complications has passed. Perhaps enforced bed rest of three weeks is ideal but in the 85 per cent or more of extremely mild cases seen nowadays this is practically impossible of accomplishment and is usually considered unjustified. Swift (1947) said that one is justified in allowing a scarlet fever patient to get out of bed when the temperature and pulse are normal, there is no leukocytosis, and the *erythrocyte sedimentation rate is fairly normal. Children will usually take* large quantities of fluid quite readily if offered in the form of lemonade

has proved the better procedure. After desquamation begins, the patient is much relieved by the application of ordinary petrolatum to which a small amount of phenol has been added, but it is well to keep the proportion of phenol below 0 5 per cent if the entire body is to be anointed; I have seen a case of mild kidney injury presumably caused by one application over the entire skin surface of an ointment containing 2 per cent of phenol. The complications must be treated as such when they make their appearance. Many physicians insist upon the most rigid isolation of the patient and the nurse, and I set down in what follows the measures through which such

') dishes to be sterilized before they are taken from the room; (e) garbage be placed on fresh newspaper outside room and immediately bundled and ed by an elderly member of the family, (f) all linens to be sterilized in room before being sent to the laundry.

'des and Penicillin.—That the sulfonamides do not affect the *ge of the disease—i.e., do not lower the fever or shorten its course,*

locality at any given time some types of streptococci have outstanding ability to produce disease, including scarlet fever, some appear incapable of causing scarlet fever but able to produce other streptococcal illnesses, and still others seem to have a general low pathogenicity.

Scarlet fever is very much more common during the first decade of life than during any other period, and though occurring sporadically it has a strong tendency to become epidemic, the seasonal incidence being greatest in the school period of September to June. It is much more often food-borne (milk or milk products) than is diphtheria, but the studies of Schwentker *et al.* (1945) strongly indicated that most cases of streptococcal infection are by direct air-borne transmission from a carrier or patient or less directly by inhalation of the organisms floating in the general reservoir of air. The generally accepted belief that people who live in rural areas are more susceptible to scarlet fever than those resident in cities was disturbed by the study of Grand and Purvis (1945), who in Dick-testing a large number of recruits failed to find any significant difference in incidence of Dick-positive reactions in the rural and urban groups. The virulence of the disease varies, mortality among children in the various epidemics being from 1.5 up to as high as 90 per cent; after the eighth year mortality rarely runs above 3 to 4 per cent, and indeed in recent years the death rate has been very low in all age groups in most parts of the world.

The typical case is characterized, after an incubation period of three to eight days, by sudden onset with nausea and vomiting, high fever, sore throat, leukocytosis, general adenopathy and the appearance within twenty-four hours of a scarlet, maculopapular ("goose flesh") rash on the body and a punctate eruption on the roof of the mouth; there is much less likely to be eruption on the face than in measles or German measles. The "strawberry"
[illegible] of the disease; nose-
toms usually begin
days after the dis-
s. It is during this
period of desquamation, which lasts for several weeks, that the secondary complications are most likely to arise; there are a great many of these but of those most frequently seen the most severe are peritonsillar and retropharyngeal abscess, cellulitis of the neck, sinusitis, otitis media and mastoiditis, nephritis and a type of arthritis which Watson *et al.* (1945) feel there [illegible] to differentiate from acute rheumatic fever. [illegible]

which death occurs from acute failure o [illegible]
toms of the disease have appeared, and [illegible]
process in the throat quickly involves the nose and the larynx and [illegible]
with death from sepsis.

A number of years ago the Schultz-Charlton test was introduced as a diagnostic aid in doubtful cases: 0.2 cc. of scarlet fever antitoxin are injected intradermally and the local blanching of the rash at the site of injection is [illegible] of the disease. Jennings and DeLamater (1947)
fou [illegible] d-
of [illegible] as
ber [illegible] nd
follows: blood is withdrawn on the day the suspect [illegible]

the serum tested for its ability to blanch a definite scarlet rash on another patient; if it does blanch the rash the patient probably does not have scarlet

fever is established, and if they do not the patient does not have scarlet

1689) has left a first-hand account, separating it from measles and giving it its present name; its confusion with measles, however, persisted for a long time after his day. Following the period corresponding roughly with the American War for Independence in the late eighteenth century, scarlet fever spread rapidly over both hemispheres and now occurs all over the world but is extremely rare among natives of Africa and India.

THERAPY

Nursing Care and Diet.—Mild cases of scarlet fever require practically no treatment, though the physician and nurse will often be greatly taxed to keep the child in bed until the danger of delayed complications has passed. Perhaps enforced bed rest of three weeks is ideal but in the 85 per cent or more of extremely mild cases seen nowadays this is practically impossible of accomplishment and is usually considered unjustified. Swift (1947) said that one is justified in allowing a scarlet fever patient to get out of bed when the temperature and pulse are normal, there is no leukocytosis, and the erythrocyte sedimentation rate is fairly normal. Children will usually take large quantities of fluid quite readily if offered in the form of lemonade Diet is usually maintained in the beginning on the liquid basis, with milk predominating, but the causal relationship of a full diet to nephritis in this disease has not been established It is now agreed that the more liberal diet has proved the better procedure. After desquamation begins, the patient is much relieved by the application of ordinary petrolatum to which a small amount of phenol has been added, but it is well to keep the proportion of phenol below 0.5 per cent if the entire body is to be anointed; I have seen a case of mild kidney injury presumably caused by one application over the entire skin surface of an ointment containing 2 per cent of phenol. The complications must be treated as such when they make their appearance. Many physicians insist upon the most rigid isolation of the patient and the nurse, and I set down in what follows the measures through which such

the room before being sent to the laundry.

Sulfonamides and Penicillin.—That the sulfonamides do not affect the toxic stage of the disease—i.e., do not lower the fever or shorten its course,

locality at any given time some types of streptococci have outstanding ability to produce disease, including scarlet fever, some appear incapable of causing scarlet fever but able to produce other streptococcal illnesses, and still others seem to have a general low pathogenicity.

Scarlet fever is very much more common during the first decade of life than during any other period, and though occurring sporadically it has a strong tendency to become epidemic, the seasonal incidence being greatest in the school period of September to June. It is much more often food-borne (milk or milk products) than is diphtheria, but the studies of Schwentker *et al.* (1945) strongly indicated that most cases of streptococcal infection are by direct air-borne transmission from a carrier or patient or less directly by inhalation of the organisms floating in the general reservoir of air The generally accepted belief that people who live in rural areas are more susceptible to scarlet fever than those resident in cities was disturbed by the study of Grand and Purvis (1945), who in Dick-testing a large number of recruits failed to find any significant difference in incidence of Dick-positive reactions in the rural and urban groups. The virulence of the disease varies, mortality among children in the various epidemics being from 1.5 up to as high as 90 per cent; after the eighth year mortality rarely runs above 3 to 4 per cent, and indeed in recent years the death rate has been very low in all age groups in most parts of the world.

The typical case is characterized, after an incubation period of three to eight days, by sudden onset with nausea and vomiting, high fever, sore throat, leukocytosis, general adenopathy and the appearance within twenty-four hours of a scarlet, maculopapular ("goose flesh") rash on the body and a punctate eruption on the roof of the mouth; there is much less likely to be eruption on the face than in measles or German measles. The "strawberry"

of the disease; nose-

toms usually begin

days after the dis-

appearance of the rash the period of desquamation begins. It is during this period of desquamation, which lasts for several weeks, that the secondary complications are most likely to arise; there are a great many of these but of those most frequently seen the most severe are peritonsillar and retropharyngeal abscess, cellulitis of the neck, sinusitis, otitis media and mastoid-

of arthritis which Watson *et al.* (1945) feel there

er.

vo definitely recognized

he fulminating type in

which death occurs from acute failure of the almost before the symptoms of the disease have appeared, and the septic type in which the anginal process in the throat quickly involves the nose and the larynx and trachea, with death from sepsis.

A number of years ago the Schultz-Charlton test was introduced as a diagnostic aid in doubtful cases: 0.2 cc. of scarlet fever antitoxin are injected intradermally and the local blanching of the rash at the site of injection is considered diagnostic of the disease. Jennings and DeLamater (1947) found commercial scarlet fever antitoxin not as reliable for the performance of this test as convalescent serum from a recently recovered patient. Goldberg and De Hoff (1942) employed a reverse Schultz-Charlton technic as follows: blood is withdrawn on the day the suspect enters the hospital and

Convalescent Serum.—It is now the consensus that convalescent serum is fully as effective as antitoxin in reducing the toxic symptoms in scarlet fever and possibly more effective in preventing complications; in addition, if properly given (see below) sensitization or unfavorable reactions do not occur. Occasionally there is an urticaria-like eruption but not true serum sickness. No blood typing or matching is required Here in Milwaukee, Fox and Gordon (1944), in a comparison of 1000 serum-treated patients with 1000 treated without serum, found that the mean days of fever duration in the controls were 5.5 and in the serum-treated cases 2.1, the duration of the disease in the controls was 43 5 and in the serum-treated 24 5, the number of deaths in the control group was 20 and in the serum-treated group 17; it should be emphasized in judging these figures that the controls were merely consecutively admitted patients with scarlet fever whereas the serum-treated cases were those sufficiently ill to justify the use of the serum. It seems unlikely that convalescent serum will hold its own against penicillin, though it should be noted that Ashley (1946), studying 298 consecutive patients admitted to a Navy Hospital during War II, found the treatment of choice to be convalescent serum administered within twenty-four hours of the appearance of the rash together with penicillin on admission and continued until the temperature had been normal for five days Fox and Gordon's dosage for infants, 10–20 cc. or 20–40 cc. for severe cases; for children, 20–30 cc or 30–60 cc. for severe cases, for adults, 20–40 cc, or 40–80 cc. for severe cases. The serum is preferably given intravenously; it may sometimes appear advisable to repeat the injection at twelve to twenty-four hour intervals.

PROPHYLAXIS

Quarantine.—The traditional rule for discharge from quarantine is that the desquamation shall be complete and that there shall be no suppurative discharges from any part of the body; moisture or discharge of any sort from the nose constitutes "discharge" though not obviously suppurative. However, it has long been recognized that the desquamating material is not infectious and that therefore the only purpose served by maintaining quarantine to the end of desquamation is to hold patients in isolation long enough for suppurations to appear. Whether patients whose scarlet fever has been complicated are more dangerous to the community following release than others is at present still a controversial question. The law in many parts of the United States requires quarantine for a minimum of four weeks from date of report, but in some areas this has been modified to two weeks for adults and three weeks for children Here in Milwaukee the period is three weeks if there are no infectious discharges or the patient is not still suffering from some other infectious complication in which discharge is not a feature; exposed contacts are kept in quarantine for one week A number of men are in opposition to present quarantine regulations and feel that when a child recovers as rapidly as is frequently the case nowadays there is no reason to hold him so long

Convalescent Serum.—Unfortunately no statistical studies of the efficacy of this agent in preventing or modifying the disease have been published in recent years. Here in Milwaukee, in 1938, Hardgrove reported that of 1001 individuals exposed to scarlet fever and given protective convalescent serum only 20 (1 88 per cent) developed the disease within fourteen days, while the office of the City Health Commissioner stated that 13 55 per cent of

or cause a diminution in the rash or an improvement in the sore throat—has now been firmly established by a large number of studies which I shall not utilize space to list here. It is conceded, however, that they are exceedingly valuable in reducing mortality when employed in the treatment of serious complications. There are some early studies indicating that their use from the beginning of an attack lowers the incidence and severity of complications, but in French's (1939) fully controlled study utilizing 340 cases, and Candel and Burwell's (1946) more recent reasonably well controlled study utilizing 303 cases, it [illegible] (1947), whose experience as [illegible] of Cook County Hospital [illegible] sulfonamides are of prophylactic value against complications At the Isolation Hospital in Milwaukee their use in uncomplicated scarlet fever has been abandoned.

But the position of penicillin seems to be much better, which is a very fortunate fact since sulfonamide-resistant streptococcal strains have undoubtedly been developing in recent years Hoyne and Brown (1947), in a large-scale study employing 548 patients, found penicillin equally as good as convalescent serum and superior to the sulfonamides, the most important advantage of penicillin being its ability to protect against complications These observers pointed out, however, that there were only a few severe cases in their series. Other series in which penicillin has been found superior to the sulfonamides in reducing the toxic state, treating complications, preventing complications and reducing the number of carriers are those of Weiss and Manheims (1946), McMillan (1946), Jennings and DeLamater (1947), and Hirsch *et al.* (1947). An example of what may be accomplished with this agent, at least in the type of relatively mild scarlet fever occurring nowadays, is indicated in the study of Breese *et al.* (1946), who gave penicillin routinely in 118 cases in a U. S. Naval Hospital during War II. All the patients showed a good clinical response, temperature dropping to normal and marked symptomatic improvement occurring in twenty-four to forty-eight hours. Only one individual failed to have a negative throat culture, and no complications developed during the course of the therapy. Breese *et al* found 480,000 units of penicillin, spread out over an eight-day period, satisfactory for treatment of the acute disease and for prevention of the carrier state in convalescents

Antitoxin.—Scarlet fever antitoxin is given intramuscularly, only in extreme cases intravenously; average dosage is 9000 units, though Wesselhoeft and Weinstein (1945) would have this doubled for patients who weigh more than fifty pounds and for those under fifty pounds who are severely ill; for severely ill patients over fifty pounds they advocate quadruple dosage. The following points I believe comprise the consensus among conservative unprejudiced observers regarding antitoxin today: (a) Early administration usually causes subsidence of fever and disappearance of the rash and other toxic manifestations, but carefully controlled studies do not show the incidence or severity of complications lessened with as great regularity. (b) The likelihood of inducing serum sickness may easily cause a longer illness than would be suffered in the average case without the treatment. (c) Severe reactions do not often occur with the concentrated antitoxins now on the market. (d) Antitoxin is almost certain to be completely superseded by penicillin.

Status of the Method—In recent years disagreements with the theoretical bases of this method of immunization and objections to its further trial have

Health Association Study Committee on Multiple Antigens):

(1) The Dick toxin, since it does not represent all the strains of streptococci associated with scarlet fever, and since equally toxicogenic strains of streptococci can be recovered from diseases other than scarlet fever, cannot form a valid basis for either a theoretically justifiable "test" or "immunization" (2) Practical justification of the test has failed to be established, since scarlet fever, frequently in a malignant form, has developed in Dick-test negative individuals Furthermore, a large proportion of positive reactions is obtained in individuals known to have had a bona fide attack of scarlet fever. (3) Most bacteriologists insist that it is not possible to induce complete active immunity against any streptococcus (4) The Dick test is much too difficult to read to be of practical use (5) Attempted immunization prevents only the appearance of the rash, thus robbing the physician of the most valuable sign of scarlet fever and preventing the isolation of these patients who have scarlet fever without rash (6) Even granting that "immunization" really immunizes, only the principal protagonists of the method claim that the immunity is a lasting one (7) The reactions to immunization are often so severe that the patient is more ill than he would be with the naturally acquired disease.

Sulfonamides and Penicillin.—In a Naval Station in which there developed a high incidence of streptococcal infections during War II, Coburn (1944) reported that the scarlet fever admission rate of 171 per 1000 strength fell

Similar striking effects were also obtained in the Army study reported by Hodges (1944) However, it is unlikely that we can make much use of such a measure in ordinary civilian practice for the reason that situations presenting the epidemiologic conditions of military life do not often arise in civilian groups Furthermore, it has been reported since the close of War II that

tory infections

In an exploration of the problem of carriers during War II, Hamburger *et al* (1945) found that nasal carriers of hemolytic streptococci are more likely to transmit infection than throat carriers with negative nose cultures And Hamburger and Lemon (1946), studying the effect of sulfadiazine and of

the unprotected contacts in the city were developing the disease within this time during the same period. Recommended prophylactic dosage is 10 cc.

serious reactions need be feared, but very mild reactions occurred in about 1 per cent of Hardgrove's cases: slight transient elevations in temperature, occasional urticaria, and joint pains lasting but a few days.

Immunization with Toxin.—This method comprises the use of the Dick intracutaneous test for susceptibility and the subsequent active immunization of "positive" individuals by the injection of multiple doses of the Dick toxin.

The Dick Test.—Inject one skin test dose of Scarlet Fever Streptococcus Toxin (0.1 cc. of the Dick test material as marketed) intracutaneously in the forearm after thoroughly cleansing the area with green soap. Inspect after twenty-two to twenty-four hours. An area of redness and slight infiltration ½ inch or more in diameter indicates susceptibility. Positive reactions fade rapidly and have usually disappeared in forty-eight to seventy-two hours but reactions that have entirely faded at the end of twenty-four hours are regarded as negative. The Dicks advise sterilization of the syringe in distilled water and rinsing of syringe and needle with the test solution before making the injection. The toxin diluted for use will retain its potency for at least two months at room temperature.

Immunization.—Five doses of the immunizing toxin are given subcutaneously in alternate arms at weekly intervals. As marketed, these doses contain:

First injection: 650 skin test doses
Second injection: 2500 skin test doses.
Third injection: 10,000 skin test doses.
Fourth injection: 30,000 skin test doses.
Fifth injection: 100,000 to 120,000 skin test doses

Reactions.—Reactions may occur after any of the doses but are most common after the third and fourth; they usually appear in six hours and in most instances have disappeared again in twenty-four hours. The following are the symptoms: nausea, vomiting, fever, scarlatinal rash, sore throat, joint pains, painful cellulitis at the site of injection, occasionally edema and rarely anasarca. Even the staunchest advocates of this method warn against its use in any child in whom one has the least reason to believe, from suggestive symptoms, that scarlet fever infection is already established; and that if a Dick-positive individual has been exposed to scarlet fever one should observe him for two or three days before starting immunization; and that no immunization ... -eight ... -dered

harbor chronic streptococcus infection at the time of the ...

Appearance and Duration of Immunity—As determined by conversion of a Dick "positive" to "negative" immunity may be demonstrated two weeks ...

probably 90 per cent of those properly injected are perman...

gitis, endocarditis, general peritonitis or pylephlebitis (all of which were almost uniformly fatal) the average death rate was only 50 per cent.

It was principally sepsis, of course, that made the hospitals of old the shambles that they were. Even as recently as the eighteenth century physicians declined hospital service "as equivalent to a sentence of death." Reforms followed the independent reports, in 1777 to 1789, of Tenon with regard to the deplorable state of affairs in the Hotel Dieu in Paris, and John Howard on numerous institutions on the Continent. However, real cleanliness only came into effect after Florence Nightingale began her labors in 1854 Lister, in 1867, inaugurated the era of surgical antisepsis that led finally to the aseptic technic And now at long last the specific chemo-therapeutic agents have effected a considerable change in the results attainable in treating the disease

THERAPY

Sulfonamides, Penicillin or Streptomycin?—In the more commonly encountered of the infections here under consideration, such as the hemolytic streptococcal, the anaerobic streptococcal and the staphylococcal, the superiority of penicillin to the sulfonamides seems to be established. Furthermore, the evidence indicates that the employment of the sulfonamides in addition to penicillin in these cases merely serves to increase the incidence of untoward reactions and complications However, in the meningococcal septicemias the superior value of penicillin is doubtful; indeed it seems likely that here, as in the meningeal infections with this organism (see Meningococcal Meningitis), the sulfonamides are still to be preferred. The infections with other organisms are best considered individually.

Pneumococcal Meningitis.—It seemed clear from the study of Appelbaum and Nelson (1945) that the introduction of penicillin has not as yet solved the problem of the treatment of pneumococcal meningitis, for this agent used alone was not effective in the majority of their sixty-seven cases However, penicillin used in combination with the sulfonamides has a better record in this disease Hartmann *et al* (1945), on the basis of experience in thirty-

duce good urine output and care is taken to maintain the urine at an alkaline pH. Smith *et al.* (1946) were able to report recovery in all of their eighteen cases treated with both drugs, and Ross and Burke (1946) in sixteen of their nineteen cases; however, in Jepson and Whitty's (1946) series of ten cases only five patients recovered, though one other survived meningitis to die of other causes

Influenza Bacillus Infections—In late 1946, Keefer *et al.*, reporting as the Committee on Chemotherapeutics and Other Agents of the National Research Council, published the statistics of the treatment of 1000 cases of various infections with streptomycin. There were 100 cases of *H. influenzae* meningitis, and of these sixty-six were cured clinically and bacteriologically while under treatment, thirteen improved under treatment and finally recovered, one improved but relapsed, three showed no effect and seventeen patients died In an analysis of the cases it appeared that the factor most unfavorable for streptomycin treatment in this infection is late treatment

employed for five to seven days in a daily dosage of 300,000 units promptly and permanently eradicated the organisms in 50 per cent of the carriers, and in the other 50 per cent eliminated it or reduced it more than 98 per cent while the penicillin was being given; in most of the carriers who relapsed in this group very few streptococci were dispersed into the environment.

SEPSIS AND THE NON-MENINGOCOCCAL MENINGITIDES

(Septicemia)

Following the example of Herrick and the frequent Continental usage, I employ the term "sepsis" for the description of a syndrome which it is more usual to designate "septicemia" in the United States. This departure is made for the reason that the term "septicemia" places too great stress upon the presence of the causative organism in the blood stream and tends to foster the misconception that this disease entity is characterized by a state of affairs in which large numbers of the organisms are constantly floating about and multiplying in the circulating fluids of the body. To be sure, eruption of the causative micro-organism into the blood stream, and perhaps a succession of such eruptions, is a *sine qua non* for the development of sepsis, but the mere

From first to last sepsis is a clinically recognizable entity, which has at some time in its course the laboratory-demonstrable feature of organisms in the blood stream; but, as Churchman so well pointed out, it is not the fact of their presence there that is of importance but rather that they have come from somewhere and are going somewhere else. The really serious fact therefore is

genitals or the female pelvis, a sore throat, otitis media, a boil or carbuncle, a compound fracture, or a serious or even a very trivial injury in which the skin is broken; in a minority of cases the original nidus cannot be located. About two-thirds of the cases are due to the streptococcus, with probably half this number caused by the staphylococcus, and the remainder by the meningococcus, the gas bacillus, the influenza bacillus, the pneumococcus, the colon bacillus, and a relatively large number of other organisms in rare instances. The onset of sepsis is usually sudden, with chill and high rise of temperature (the type of which varies somewhat with the organism involved) and rapid pulse and respiration, sweats, frequently gastro-intestinal symptoms, leukocytosis, multiform skin lesions and a nervous involvement varying between the extremes of wild delirium and coma. What metastatic involvements are to supervene cannot be predicted in the beginning; meningitis, endocarditis, suppurative arthritis and embolic phenomena are among those that most frequently occur. Some patients die very quickly from an overwhelming toxemia, others linger only to succumb after several weeks or even months. In the days before the advent of the specific chemotherapeutic agents, Tileston placed the general mortality at 60 to 80 per cent, Herrick at 70 to 90 per cent; the latter stated that if one eliminated cases with menin-

but in Morgan and Hunt's (1946) case of *S. suipestifer* empyema and bacteremia both streptomycin and penicillin failed. Of the twenty-six patients in the series of Keefer *et al.* (1946), treated for various salmonella infections with streptomycin, fourteen had bacteremia; ten recovered under treatment, two showed improvement and recovered later, six showed no improvement and eight died. In only one patient who recovered under treatment was streptomycin started after the eighth day of illness. The high total fatality rate in these cases would certainly indicate that if good results are to be achieved here maximum doses of streptomycin must be used very early. The sulfonamides have occasionally been effective in salmonella meningitis.

Pyocyaneus Infections.—Morgan and Hunt (1946) reported the case of a man with *Ps. pyocyanea* sepsis from whom only one positive blood culture was obtained a few hours after the beginning of streptomycin therapy; both penicillin and sulfadiazine had been previously administered without effect; the recovery was rapid and complete However, both Cairns *et al.* (1946) and Stanley (1947) reported the unsuccessful employment of this agent, Cairns in three cases of meningitis and Stanley three of sepsis, the latter feeling, however, that the presence of associated disease influenced the outcome in each of his cases. Keefer *et al.* (1946) included ten pyocyaneus infections in their 1000 streptomycin-treated cases, there were six recoveries.

Other Organisms.—The following responses to streptomycin were recorded by Keefer *et al* : *Pr. vulgaris*, five cases with recovery in five; *Aerobacter aerogenes*, six cases with recovery in four; *Str. faecalis*, three cases with recovery in two; *Enterococcus*, two cases with recovery in two; *Neisseria*, one case, fatal; *E. coli* and *Str. faecalis*, one case, fatal; *E. coli* and *A. aerogenes*, one case, no effect; *Ps. pyocyanea* and *A. aerogenes*, one case, recovery; *E. coli*,

organism the dose may have to be doubled and perhaps the time intervals between injections reduced to three or even two hours.

The *Romansky formula*, containing 300,000 units (preferably the crystalline penicillin G preparation that may be stored at room temperature) in peanut oil containing 4 8 per cent beeswax has been shown by ample experience to be effective against the more susceptible organisms in a single daily intramuscular

beta-hemolytic streptococcus, for clinical observation reveals continuing effect against sensitive organisms even though blood levels have fallen below assayable titers. Romansky and Rittman (1945) found that very little is gained by using larger amounts than 300,000 units at a single injection, but that if this same dose is simply reinjected at twelve hours the titer maintained continuously will take care of practically any of the infections under present consideration.

after other forms of therapy have failed. Alexander *et al.* (1946) felt, from their experience in twenty-five cases of this type of meningitis, that streptomycin alone will bring about complete recovery in cases of average severity but that when the infection is severe it is advisable to use sulfadiazine and rabbit antiserum as well as streptomycin. They recognize that to increase the number of survivors in these severe cases may serve to increase the incidence of mentally defective children, but they were not certain that this had been proved as yet. Nussbaum *et al.* (1946) reported the concomitant employment of streptomycin and sulfadiazine in three cases of influenzal meningitis in children less than two years old with recovery without complications or sequelae in all three cases In the case of a child with bacteremia, meningitis and cerebral abscesses due to *H. influenzae*, reported by Morgan and Hunt (1946), streptomycin cleared the blood and spinal fluid of organisms, but the spinal fluid again became positive and the organism was found to have acquired marked resistance to streptomycin; use of the agent was then discontinued and the patient slowly recovered after treatment with specific antiserum, sulfadiazine, penicillin and aspiration of the cerebral abscesses. In discussing the treatment of these *H. influenzae* cases, Weinstein (1946) stressed the occurrence of superinfections with organisms resistant to streptomycin but sensitive to penicillin; he strongly recommended the concomitant use of penicillin as soon as the staphylococcus becomes the predominant organism in the nasopharynx even before there is evidence of systemic invasion. The record of penicillin and the sulfonamides, without streptomycin, is not altogether bad: of the five patients treated by Zinnemann (1946) with sulfonamides alone only one recovered, but of his other fifteen patients, who received both penicillin and sulfonamides, eight recovered.

Friedlander Bacillus Infections—Kobacker and Mehlin (1945) reported the successful treatment of a very severe infection with *Kl. pneumoniae* with penicillin; a pharyngeal abscess was the initial focus, bacteremia complicated the condition, and there was probably early cavernous sinus phlebitis and a secondary bronchopneumonia In Morgan and Hunt's (1946) case of this type of pneumonia there was no response to penicillin; the patient was stuporous, irrational and desperately ill when streptomycin was begun, but within forty-eight hours marked improvement occurred and recovery eventually took place. The report of Keefer *et al.* (1946) included two cases of Friedlander pneumonia with two recoveries. The patient of Tartakoff *et al.* (1946) died of pulmonary embolism incident to thrombophlebitis of the lower extremities while being treated with streptomycin; at autopsy there was found no gross and almost no microscopic evidence of meningitis although clinically the patient had been recognized as having Friedlander bacillus infection with signs of overwhelming meningeal involvement.

Colon Bacillus Infections.—In the Keefer *et al.* (1946) report on the employment of streptomycin there were thirty-four cases of *E coli* infection with recovery in twenty-five. Morgan and Hunt (1946) reported the unsuccessful use of streptomycin in a case of *E. coli* sepsis in which penicillin had also failed; the blood cultures were rendered sterile but the patient nevertheless died and at autopsy there were found multiple lung and spleen abscesses from which *E. coli* was cultivated.

Salmonella Infections—Janney *et al.* (1947) reported the successful use of streptomycin in a case of *S manhattan* meningitis in an infant one month old,

mococcal meningitis in a patient treated with penicillin intrathecally. The latter patient had been given daily intrathecal injections ranging from 10,000 to 40,000 units, and in his discussion of the case Siegel said he believed that in the fulminating meningitides greater emphasis should be placed upon the use of larger doses of intramuscular penicillin and that when the agent must be used intrathecally it would perhaps be well to limit the dosage to not more than 10,000 units at each injection. Actually, intrathecal penicillin dosage has usually ranged between 10,000 and 30,000 units for a single injection, but some men have used considerably more: for example, Reitz (1946) reported eight cases of meningitis, two pneumococcic and six meningococcic, in which several of the most critically ill patients received single doses of 100,000 units every twelve hours for three doses. One of these patients received two injections of 100,000 units each, five hours apart, and a third injection of the same size the next day No untoward reactions were reported in these cases of Reitz The British, however, seem to be adhering to lower dosage, for Jepson and Whitty (1946) referred to 10,000 to 20,000 units as an "overwhelming intrathecal dose of penicillin," and Smith *et al* (1946) stated that dosage of 40,000 units and over may produce severe reactions when injected into the ventricles, or damage to the cauda equina or gumming of the subarachnoid space when injected by the lumbar route. In our own country, however, Reuling and Cramer (1947) said that they have repeatedly used 50,000 units per single intrathecal injection in various types of meningitis without damage to the cauda equina or subarachnoid space These latter observers reported the case of a patient who had received in error 500,000 units instead of 50,000 units intrathecally; recovery occurred promptly after a series of convulsions Harris *et al* (1946) reported the unique occurrence of secondary *B pyocyaneus* meningitis following intrathecal penicillin treatment for pneumococcus meningitis in four patients, two of whom died, the source of the *B. pyocyaneus* was traced in two of the cases to penicillin solutions contaminated by syringes used to withdraw the drug for injection

The reactions twice elicited in the patient of Johnson and Walker (1945), given penicillin *intraventricularly*, comprised coma, vascular collapse and clonic spasms and caused these observers to suggest that penicillin be administered intraventricularly only in small amounts and with caution.

Penicillin has been successfully used *intrapericardially* A typical case was that of Smith and McHugh (1945), whose patient with meningococcal pericarditis not responsive to pericardial paracentesis and massive sulfonamide therapy had 10,000 units of penicillin in 10 cc of saline instilled into the pericardial space twice on successive days after the withdrawal of a large amount of turbid fluid. Improvement was rapid, intramuscular penicillin being also used after the first intrapericardial injection was made.

Penicillin Reactions.—See separate chapter at end of book.

Streptomycin Dosage and Toxicity.—See in Tuberculosis.

Sulfonamide Dosage.—See in Pneumonia.

Sulfonamide Toxicity.—See separate chapter near end of book.

Specific Antiserums.—Ross and Burke (1946) felt it difficult to appraise the value of type-specific antiserum as an adjunct to sulfonamide-penicillin therapy in their relatively small series of pneumococcus meningitis, but it was Appelbaum's (1945) experience that such serum contributed little to the recovery of any of his patients However, in cases of influenza bacillus

meningitis the type-specific *H. influenzae* antiserum developed by Alexander has been very useful. Alexander (1944) gives sodium sulfadiazine subcutaneously in a dosage of 0.1 gm. per kilogram body weight and then administers the serum intravenously in dosage dependent upon the concentration of glucose in the spinal fluid prior to the beginning of treatment: *i.e.*, for a spinal fluid sugar under 15 mg. per 100 cc., 100 mg. of antibody nitrogen (150 mg. for a child over three years of age) is given; for a blood sugar of 15 to 25 mg. per 100 cc., 75 mg.; 25 to 40 mg. per 100 cc., 50 mg; and over 40 mg. per 100 cc, 25 mg The sulfadiazine is repeated at twelve-hour intervals for at least two doses and further dosage is administered by mouth, together with fluids and alkalis, in amounts depending upon the response of the patient. Alexander treated eighty-seven patients either in the Babies Hospital in New York or under her close supervision in other institutions with this combined sulfonamide and *H. influenzae* serum regime; 78 per cent of the patients recovered completely. Beck and Janney (1947), reviewing forty-seven cases treated according to Alexander's directions, felt the serum-sulfonamide method to be 85 per cent effective when instituted before the patient is moribund. Edmonds and Neter (1946) also had good results in a series of sixty cases, but they felt that in certain selected patients intrathecal serum administration may be beneficially used to supplement intravenous therapy, though they recognized that intrathecal injection may be harmful to patients whose spinal fluid contains many bacilli. Smith *et al.* (1946) felt that the intramuscular route should be used more often for the introduction of the serum as it obviates some of the severe reactions observed after intravenous administration.

[illegible] to rest the bowel the diet should [illegible] maintained [illegible] enema of [illegible] onade are [illegible] th. When the patient is vomiting it is often advisable to discontinue the attempt to supply food and fluid by mouth and to resort to the intravenous administration of dextrose, either occasionally or by the continuous drip method (venoclysis). If the dextrose solution is prepared with physiologic saline or preferably Locke's solution, the loss of chlorides occurring in excessive [illegible] Hypo- [illegible] d [illegible] f [illegible] the sulfonamides retained when administered by mouth, the introduction of a Levine duodenal tube for continuous drainage of the stomach (with suction if necessary) may be helpful

Elimination of Foci.—Attempts to halt the influx of organisms into the blood stream through the elimination of primary or secondary foci are surgical matters outside the province of this book.

SHIGELLOSIS

(Bacillary Type of Dysentery)

in temperature, severe abdominal pain and tenesmus, early appearance of bloody and mucous diarrhea, and the symptoms of toxemia and dehydration. There is diffuse inflammation of the colon and lower part of the ileum, with ultimately necrosis and extensive ulceration and very rarely perforation. Adults between twenty and thirty and infants under two years of age are the most susceptible. The disease is endemic in the tropics and occurs sporadically elsewhere, but it may become epidemic anywhere during periods of crowding, bad sanitation, privation and other causes not yet understood. Flies, ants

active military operations Mortality varies widely with the locality and the particular outbreak, being from 2 to 60 per cent with an average in the United States of 2½ to 5 per cent Death is caused by toxemia, or later in the disease by peritonitis or inanition, circulatory failure or intercurrent pneumonia is

not at all too high. Felsen (1945) also estimated that 3 to 10 per cent of all patients who have had acute shigellosis become chronic carriers of the organism, indeed, even individuals with no history of recent infection and no intestinal complaints have been shown to be carriers to a greater extent than was formerly believed, Watt *et al.* (1942) found 2 per cent of carriers among 6324 such individuals in New York City and 3 2 per cent in 1650 persons examined in New Mexico, Georgia and Puerto Rico

THERAPY

Sulfonamides—*Efficacy* —During War II there accumulated considerable evidence in favor of the value of sulfonamides in shigellosis In the controlled study of Painton and Hantman (1945), in a training center in the United States, the sulfonamide-treated group responded much more rapidly than that treated symptomatically, Scadding (1945) recorded the clinical impres-

Nevertheless, there are those who very much doubt the value of the sulfonamides in shigellosis: witness the adverse reports of White *et al* (1946), who

treated an outbreak aboard a U. S warship in Philippine Waters, and Elsom *et al.* (1946), whose experience was gained in an Army general hospital in India. So nearly as I can determine it from the rather confusing literature, the fact seems to be that mild cases of shigellosis tend strongly to be self-limited and probably derive no advantage from being treated with the sulfonamides, whereas in the severe cases the efficacy of these drugs is almost certainly established. Smith (1946), writing of cases treated in New Guinea, stressed the point that while effective early treatment with sulfonamides usually leads to prompt or dramatic cessation of diarrhea and cramps, this symptomatic relief *is not paralleled by objective healing of the mucosal lesions, which indeed may* require three days to three weeks or longer depending upon the length of time elapsing between the onset of symptoms and the institution of therapy.

Choice of Preparation —Of the three poorly absorbed sulfonamides—sulfaguanidine, sulfasuxidine and sulfathalidine—the first is no longer used whenever either of the others is available for the reason that it is sometimes absorbed rather erratically and its conjugated form is relatively insoluble in the urine and may therefore at least theoretically give rise to urinary tract disturbances. For example, in the study of Smyth *et al.* (1943), in twelve sulfaguanidine-treated cases there were two instances of concentrations a little above and a little below 8 mg. per cent, one instance of 10 mg. per cent, one of 14.3 mg per cent, and one of 16 6 mg. per cent, whereas in the twenty-four sulfasuxidine-treated cases in no instance did the concentration exceed 1 45 mg *per cent. In the sulfathalidine-treated patients of Poth and Ross (1944)* blood levels as high as 3.2 mg. per cent were recorded, but it was said that ordinarily the concentration does not exceed 1 5 mg. per cent. The new drug sulfacarboxy- ... said to be so poorly absorbed that

observed; but not a great deal of experience has been had as yet with the drug Hardy (1945), of the U.S P.H S , made a thorough comparative study ... of those mentioned above except the newest

... arie-

... acy,

... the

do not seem effectively to reach the bacteria within the intestinal ... Watt and Cummins (1945) used three of these easily absorbed compounds—sulfadiazine, sulfapyrazine and sulfamethazine—in the treatment of 333 routinely hospitalized cases of acute shigellosis, *all three were therapeutically* active in about the same degree, but sulfamethazine was found more toxic than either of the other two It would therefore seem that here, as in most other situations in which one must choose among the sulfonamides, sulfadiazine comes out the winner.

Dosage.—Nothing has happened since 1945 to warrant alteration in the dosage of sulfadiazine and sulfathiazole recommended in the War Department Technical Bulletin of that year, which was an initial dose of 2 gm. followed by ... minimum of ... ecovery, the ... four times

daily and it was considered permissible alternatively to administer 3.5 gm. of *sulfaguanidine every four hours day and night. Sulfathalidine is ordinarily* given in half the dosage of sulfasuxidine or sulfaguanidine.

Saline and Dextrose.—It is of course of great importance to combat the dehydration and acidosis and salt deprivation which occur with astonishing rapidity in fulminating cases, even though the sulfonamides are being administered. Parenteral administration of dextrose in Locke's solution is the best way to combat these conditions, but if acidosis is severe it may be advisable to

chloride 0 2 gm.

Shock and Anemia.—The handling of shock is discussed in a special article (see Index). In a rapidly fulminating case it may be necessary to administer a transfusion of whole blood before instituting any other treatment, for the blood loss and consequent anemia may be very great.

Pain.—Abdominal cramps and tenesmus are treated with bismuth subcarbonate, opium and heat to the abdomen. Thompson and White (1946) found the following an excellent suspension of bismuth subcarbonate:

	gm or cc
Corn starch	37 0
Simple syrup	370 0
Bismuth subcarbonate	130 0
Essence of peppermint	1 0
Water (to make)	1000 0

Mix the starch in 50 cc cold water to form a smooth paste Heat the simple syrup and 250 cc of water to boiling, then quickly add the starch mixture and continue to heat for 15 minutes Mix the bismuth with 125 cc. of water to *form a smooth paste Strain mixture of cooked starch through crinoline and* add bismuth mixture Mix Add peppermint and sufficient water to make 1000 cc

This preparation was given orally in doses of 1 ounce (30 cc) every four hours day and night, and two hours after each dose of bismuth 12 minims (0.75 cc.) of deodorized tincture of opium was given In some cases of severe tenesmus, Thompson and White employed the following with good effect:

	gm or cc
℞ Scopolamine hydrobromide	0 006
Tincture of belladonna..	15 000
Aromatic elixir (to make)	120 00

Directions One teaspoonful every three hours

Lavage of the rectum with small quantities of warm physiologic saline solution seemed to hasten the recovery and reduce residual proctospasm in cases that had passed through the acute diarrheal stage of the disease, in the experience of the above observers

Polyvalent Serum.—Even before the advent of the sulfonamides it was the consensus that in mild cases likely to recover quickly the cost of the serum plus the probability of serum sickness contraindicated its use, while in severe cases it was by no means agreed by all authorities that serum treatment of the cases effect
results are to be expected in
exotoxin is produced. Forty
may be given intravenously or in less fulminating cases the same dosage undi-

luted intramuscularly. It is said to be advisable to repeat the dose twice daily until signs of toxicity such as delirium or apathy have disappeared.

Convalescent Serum.—Felsen (1945) advocated the subcutaneous administration of 50 to 100 cc. of pooled convalescent serum (adult dosage) within the first twenty-four hours, or the administration of the same amount intravenously if compatibility tests permit. He collects blood from convalescent acute cases at about the end of the third week.

Bacteriophage.—According to statements of German medical officers during War II, bacteriophage was the standard treatment for bacillary dysentery in the forward areas of the German army in Africa. Large quantities of this bacteriophage were captured during the Axis retreat from El Alamein, and Boyd and Portnoy, in 1944, made a valuable controlled study of its efficacy on German prisoners. It was concluded from this study that bacteriophage fails to exercise *in vivo* the potent properties which it exhibits *in vitro*. In a later study, Painton and Hantman (1945) also found bacteriophage ineffective

Diet.—It is difficult to make any distinction between dietary treatment here and in acute severe cases of amebiasis except in the one item of milk,
given, whether fresh, diluted, or disguised,
icken broth must be substituted The ex-
ımebic dysentery diet should be eliminated
in sev
rhea.
supple
et al. (1939) had good success with pectin-agar (see Index).

Nursing Care.—The patient must be kept as quiet as possible since the very frequent stools are terribly wearing even in the absence of toxemia. To keep him warm will sometimes tax the ingenuity of nurse and physician Isolation and scrupulous attention to the personal hygiene of patient and attendants are fully as important here as in typhoid fever.

The Carrier.—There have been a number of reports of the successful sterilization of carriers of Shi
sulfa-
suxidine in full treatment dosa
(1943) is typical: they treated
with sulfasuxidine daily for six days; dysentery bacilli disappeared
feces of every patient, the criterion of cure being a minimum of nine consecutive negative reports of feces cultures begun on the fourth day following cessation of treatment.

PROPHYLAXIS

Sulfonamides.—In the study of Yannet *et al.* (1944) after the outbreak of Sonne dysentery in an institution housing girls of an average age of seventeen years, twenty-two girls were placed on sulfaguanidine at 2 gm for fourteen days and thirty-one were left untreated as controls, all the girls eating in a common dining room and using common play rooms and bathrooms; six girls in the control group developed typical dysentery and none in the treated group That the organisms may become "fast" to the sulfonamides was indicated in the study of Cheever (1946), who felt that this might be a possible explanation for the relative inefficacy of sulfadiazine prophylaxis in his epidemic since the organism with which he was dealing was found to be distinctly resistant *in vitro*.

Vaccine.—The thoroughly performed study of Shaughnessy et al. (194?) failed to reveal that polyvalent dysentery vaccine has any value in pre- [illegible] and Opper (194?), the incidence [illegible] ith vaccine was slightly, though [illegible] comparable control group.

SINUSITIS, OTITIS MEDIA AND MASTOIDITIS

ACUTE PARANASAL SINUSITIS

The anterior group of sinuse[illegible] the frontal, the anterior eth[illegible] maxillary antrum—open into [illegible] nate: the posterior group—p[illegible]

does not by any means always effect amelioration. Similarly there is disagreement among rhinologists regarding the advisability of routinely removing simply hypertrophied tonsils and adenoids in these cases, though the consensus seems to be that if "septic" they should come out.

Reducing Congestion.—It is probable that the most important aim of treatment is to facilitate drainage from the sinuses by reducing congestion of the mucous membranes about the openings into the meatus and it is just this thing which we are not often able to accomplish satisfactorily. Not that the mucosa cannot be shrunk—nothing is easier really—but to do it without causing a reaction of turgescence or greatly slowing or stopping entirely the movement of the cilia of these membranes, there lies the difficulty. Investigation of the cilia which sweep all secretions back toward the esophagus has disclosed that any measures which retard their movement are apt to postpone the patient's recovery from an acute attack or convert the condition into a case of chronic sinusitis The following measures are discussed with this in mind.

Sprays and Drops.—The investigations of a number of workers since 1933 (see *Lierle and Moore, Proetz, McMahon, Fenton and Larsell, Walsh* and Cannon, and Cannon, in Bibliography) have indicated a number of surprising [illegible] In brief the obser- [illegible] effect [illegible] stop [illegible] markedly slows it. (c) From [illegible] n chloride [illegible] 00 in normal saline slows or paralyzes and so does cocaine in more than 2.5 per cent strength. (e) Mild silver proteins of the type of argyrol and neosilvol are incompatible with the salt solution and when used in water definitely slow the ciliary activity. Ten per cent concentration of these drugs in contact for twenty minutes with the mucosa of the frontal sinuses of the dog caused edema and intense cellular concentration throughout the mucosa and actual fragmentation of the columnar epithelium. (f) Eucalyptol, menthol, thymol, zinc sulfate, mercurochrome and merthiolate all cause slowing or paralysis of ciliary activity depending upon their concentration. (g) Oily vehicles are dangerous from the standpoint of liability to induce lipoid pneumonia, and some much used agents, such for example as the mild silver proteins, are also prone to cause comparable pulmonary tissue reactions.

Therefore. of the astringents principally used—cocaine, epinephrine (adren- [illegible] advisable [illegible] armful [illegible] ntains [illegible] ed by 1 per cent of the active drug in 0.9 per cent saline, it may be [illegible] boiling and will then keep for many months without the addition of a preservative·

℞	Ephedrine sulfate	gr xx	1 2
	Sodium chloride	gr. xvij	1 0
	Water to make	℥iv	120 0

Label· Use as nose spray or drops as directed.

Parkinson (1936, 1939) strongly advocated the "lateral head-low posture" in introducing drops into the nose. Reference to the diagrammatic sketch will

Surgery.—When, despite treatment such as outlined in the preceding

of the patient

Otitis Media

When infection spreads into the eustachian tube this passageway quickly becomes occluded by the swelling of its mucosa and products of inflammation accumulate thereafter in the infected atrium or lower cavity of the middle ear. In most instances it seems that the curtains of swollen mucous membrane which separate the attic with its contained ossicles from this lower

waiting for the severity of the involvement to become manifest. Opiates seriously mask the symptoms and should not be used, but ear drops such as the following are much employed

℞ Phenol	gr. xxv	1 5
Glycerin	℥j	30 0

Label Warm and introduce 3 to 5 drops in ear every 2 or 3 hours

Hot applications, in the form of the electric pad, hot water bottle, or poultices will also bring much relief and aid in "pointing" the process. The linseed poultice (see Index) retains heat a long time but its weight on the ear is sometimes objectionable.

Incision (Paracentesis).—As pressure of the pus increases so does the pain and in young children fever often rises quite high, adults may remain afebrile but will complain of noises in the head and deafness on the affected side. The landmarks disappear from the ear drum, the light reflex is lost, and the drum becomes dark red and begins to bulge. Now arises the question, should incision be made at once? I know that the almost unanimous "yes" of the rhinologists seems to supply a very definite affirmative answer, but perhaps the point is a bit finer than this. Is it not true that the cases which rupture spontaneously usually do so before the practitioner has had much time to ponder the question to cut or not to cut, and that the frequent neces- to add an incision even after the rupture indicates a quite fulminant in these infections? Of course the query cannot be answered because when it bulges" is so much the rule nowadays (even a normal infant's

as follows: "Equal parts of phenol, menthol, and cocaine hydro- used. This thin paste is applied sparingly with a small cotton the bulging area of the ear drum. It is well to warn the patient ouch hurts The swab is held in place as long as the patient can s usually a few seconds. The same procedure is continued until contact the inflamed ear drum without much discomfort . The incision is then made through the bulging area of the hould appear white if properly anesthetized, with a light

the use of the benzedrine inhaler but that it should be used cautiously if at all in patients with angina pectoris since in occasional cases it may precipitate an attack. I would point out that their findings indicated nothing with regard to frequent inhalation over a long perod.

A prescription for drops, much used by rhinologists (Reese), is the following:

℞ Cocaine (alkaloid)	gr. j	0 06
Camphor	gr. j	0 06
Oil of cinnamon	♏j	0 06
Liquid petrolatum to make	℥j	30 00
Label. Drop into nose as directed.		

The amount of cocaine here (less than 0.25 per cent) is not sufficient to check

that they may quickly make their way into the lungs and there set up a lipoid pneumonia; one wonders if merely the cocaine in normal saline might not be just as effective without having any deterrent action—a prescription such as the following:

℞ Cocaine (alkaloid)	gr j	0 06
Sodium chloride	gr. ivss	0 27
Water to make	℥j	30 00
Label Drop into nose as directed		

The introduction of cotton-tipped applicators or tampons soaked in stronger cocaine solutions seems inadvisable in the present state of our knowledge; at

omission, while if he must ultimately be referred ... specialize in the treatment of these cases in the chronic stages one may be sure that he will thenceforward be probed to repletion.

Local Chemotherapy.—It does not seem to me that the value of *penicillin* when locally applied in sinusitis has as yet been determined. Vermilye (1945) stated that it is important to precede the use of aerosolized penicillin with application of a vasoconstrictor (see a preceding page for formula). He also found it necessary in some cases of chronic suppuration of the sphenoids or ... to wash out the pus by catheter and then introduce the penicillin

displacement technic, was disappointed in the results. ... Barach *et al.* (1946) of an apparatus designed to deliver penicillin aerosol with intermittent negative pressure in the nasal and postnasal pharynx may ... record that ... micro- ... became

crystals of sulfathiazole has been ... generally available this older therapy was immediately and practically completely replaced by the newer. Claims that the addition of sodium sulfite to the solution to make it stable to light, air and heat, and the further additi... or a 1 per cent aqueous solution c... efficacy of the sulfathiazole, have ... of most men.

Surgery.—When, despite treatment such as outlined in the preceding pages, the pain and headache increase, temperature rises, and the surrounding tissues begin to swell, it is felt by many that resort to surgery should be had; at least otorhinologic consultation at this time may be to the advance of the patient.

Otitis Media

When infection spreads into the eustachian tube this passageway quickly becomes occluded by the swelling of its mucosa and products of inflammation accumulate thereafter in the infected atrium or lower cavity of the middle ear. In most instances it seems that the curtains of swollen mucous membrane which separate the attic with its contained ossicles from this lower space are not easily penetrated, so that rupture and escape through the less resistant ear drum take place if the inflammatory process continues for long or if pus accumulates quickly in large amount.

Analgesic Treatment.—In the beginning, relief of pain is indicated while waiting for the severity of the involvement to become manifest. Opiates seriously mask the symptoms and should not be used, but ear drops such as the following are much employed

℞	Phenol	gr. xxv	1.5
	Glycerin.	℥i	30.0
	Label: Warm and introduce 3 to 5 drops in ear every 2 or 3 hours		

Hot applications, in the form of the electric pad, hot water bottle, or poultices will also bring much relief and aid in "pointing" the process. The linseed poultice (see Index) retains heat a long time but its weight on the ear is sometimes objectionable.

Incision (Paracentesis).—As pressure of the pus increases so does the pain and [illegible]
but [illegible]
The [illegible]
the [illegible]
should incision be made at once? I know that the almost unanimous "yes" of the rhinologists seems to supply a very definite affirmative answer, but perhaps the point is a bit finer than this. Is it not true that the cases which rupture spontaneously usually do so before the practitioner has had much time to ponder the question to cut or not to cut, and that the frequent necessity to add an incision even after the rupture indicates a quite fulminant quality in these infections? Of course the query cannot be answered because "incise when it bulges" is so much the rule nowadays (even a normal infant's [illegible]

[illegible]

the applicator can contact the inflamed ear drum without much discomfort for a minute or two. The incision is then made through the bulging area of the ear drum, which should appear white if properly anesthetized, with a light

paracentesis knife. If there is no bulging, the incision is made in the posterior

toward the ear drum until the point of the knife gently strikes the promontory without harm. I have found no need for extensive incision of the ear drum. If the tympanum continues to fill with pus, the small incision enlarges with the infection. If drainage is slight, the small or large incision closes quickly and another opening may be required."

General Anesthesia.—Ethyl chloride sprayed on an open mask over the nose and mouth is satisfactory for one experienced with this useful anesthetic; or vinyl ether (vinethene) may be used by the drop method. Of course nitrous oxide-oxygen is ideal but expensive and often unobtainable for a patient quarantined by the primary infection.

Treatment after Incision.—With the establishment of free drainage pain

from the external auditory canal and prevent irritation of the external ear. Rhinologists are divided in their allegiance to wet or dry methods of accomplishing these results, so I shall describe them both.

Wet Treatment.—Immediately after operation or rupture a gauze wick is carried in as far as the opening in the drum and replaced frequently during about forty-eight hours. Then irrigation is instituted with the following approximately saturated solution of boric acid as hot as can be borne (about 110° F.); the soda aids in dislodging a sticky discharge but may be omitted:

℞	Boric acid	ʒx	40 0
	Sodium bicarbonate	ʒx	40 0
	Water to make	Oij	1000 0
	Label Use for irrigation of ear		

The irrigations should be performed gently, with the ear held downward over a pan, and repeated three or four times daily. Between treatments a wick may be kept in the canal or the phenol-glycerin drops (see above) may be diluted with an equal quantity of boiled water and instilled. Some men prefer to swab the canal dry after the irrigation while others do nothing, a gauze pad may be applied over the external ear and conveniently held in place by a hair net tied under the chin.

canal with cotton-tipped applicators and the avoidance of irrigation; in this method it is sometimes the practice to dip the swab in the following solution before introducing it into the ear:

℞	Boric acid	gr xl	2 4
	Alcohol	℥j	30 0
	Water to make	℥ij	60 0
	Label Use in swabbing ear		

... to blow powder into the ear after the swabbing, believing

℞ Iodine (Crystals) .... gr. v 0.3
Boric acid .... ʒj 30 0
Dissolve iodine in alcohol, make into paste with the boric acid and dry to a powder
Label To be used in ear as directed.

Protecting External Ear.—Dermatitis may arise as a result of the irritating effects of the discharges. Washing the ear once or twice daily with normal saline (in the home, a teaspoonful of salt to the pint of water) and keeping it covered with a layer of zinc oxide ointment U.S.P. will likely prevent this.

cured after the onset of the discharge, and 11.7 per cent went on to acute mastoiditis. Of the sixty mastoiditis cases, 45 per cent were cured by systemic treatment with penicillin and did not require surgery. In twenty-nine of the thirty-three cases of mastoidectomy the results were excellent, 8 2 days being required for healing of the postaural incision and an average of 7.4 days for clearing of the middle ear and healing of the tympanic membrane, this being about one-third of the time required for the accomplishment of these objectives without the use of chemotherapy. It was said that not a single case of chronic discharging ears followed treatment of these cases. Allman also included in his report seventeen mastoidectomies on patients with non-scarlet fever mastoiditis, with results that were just about the same or perhaps even a little better In Weinstein and Atherton's (1945) series of cases, bacteriologic studies of the purulent exudates revealed hemolytic *Staphylococcus aureus* alone in 22 per cent, the beta-hemolytic streptococcus alone in 42 per cent, the nonhemolytic *Staphylococcus aureus* alone in 20 per cent, the beta-hemolytic streptococcus and hemolytic *Staphylococcus aureus* in 10 per cent, the beta-hemolytic streptococcus and nonhemolytic *Staphylococcus aureus* in 4 per cent and *Corynebacterium diphtheriae* and nonhemolytic *Staphylococcus aureus* in 2 per cent. Under penicillin these organisms disappeared fairly rapidly in most instances, but *Staphylococcus aureus* persisted for a considerably longer time than did the beta-hemolytic streptococcus.

Urethane and Sulfanilamide Locally—Gram-negative organisms such as *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Hemophilus influenzae* are known to be insensitive to the action of penicillin, therefore otitis media due to or complicated by infection with these organisms is not controlled by penicillin therapy. In the series of Weinstein and Atherton (1945), gram-negative bacteria appeared in the purulent exudate in the ears of four of the patients. These patients all responded quickly and completely to instillation of 4 drops of a sterile aqueous solution of 10 per cent urethane and 1 per cent sulfanilamide into the external auditory canal every three hours, the purulent exudate being first removed by means of sterile gauze wicks.

Sulfonamides.—While it seems that penicillin is destined to replace the sul-

three days in the vast majority of cases. (c) The patients recovered a week earlier on the sulfonamide compounds and the incidence of mastoidectomy *was reduced by two-thirds.*

"Masking."—Under the sulfonamides, though apparently much less frequently under penicillin, a patient's discharge may cease without mastoid tenderness having ever appeared; the drug will be stopped and he will be discharged, only to have him come back after some days with a high temperature and signs of serious mastoid involvement. *The only remedy I have heard of or* seen for this state of affairs is to persist in the use of the drug for several days after disappearance of symptoms before signing the patient out. Another feature of this new chemotherapy is that under adequate dosage the clinical picture may indicate improvement while the mastoid bone is being involved with few or no signs or symptoms to indicate it; the otolaryngologists call this "masking." Some men say that in doubtful cases it is well to stop administration of the drug for a while in order to get the true clinical picture.

Mastoiditis

When a surgical consultant concludes that the mastoid is involved he will usually have had the following points in mind as he made his examinations. (a) Tenderness over the antrum from the very beginning is not unusual but *it typically stops when good drainage is established;* if it continues and grows worse it means serious mastoid disease. (b) When mastoid pain begins after the ear has been discharging painlessly for two or three weeks it is indicative of acute mastoiditis; such pain appearing after the discharge *has ceased has* the same meaning. (c) Mastoid pain is usually worse at night. (d) A profuse discharge persisting and with pulsation is of serious moment (e) In adults with mastoid involvement there may be little tenderness.

When in the surgeon's opinion operation is indicated every effort should be *made to win the family's early consent* because a delay may endanger life, *whereas with an operation performed in time the usual result* of the mastoid complication is only to postpone somewhat the ultimate and complete recovery.

SMALLPOX

Smallpox has doubtless existed since the earliest times in China, India, Africa and the Mediterranean littoral, though there is *considerable* doubt [illegible] it was described by the Greeks or even the early Romans. Green- [illegible] [illegible]d not reach England [illegible] hemisphere *(Mexico)* [illegible]t medical publication *in North America* dealt with smallpox (Thacher's Brief Rule to Guide, etc.," Boston, 1677). According to Russell (1940) the disease did not reach Hawaii until 1853, when it promptly carried off 8 per cent *of the population* The malignant "classical" *form (variola))* still holds ravaging sway in the hinterland of the less enlightened countries, with a mortality of 25 to 35 per cent. According to Workman (1946), the wide-spread and severe epidemic of this form of smallpox in the native popula*tions of Japan* and Korea following the conclusion of War II had a mortality in our service personnel of approximately 30 per cent. In well vaccinated lands, such as certain of the

is a second rise in temperature which coincides with the pustular stag the eruption. This second period of fever terminates with the beginnin desiccation, about the twelfth day of the eruption, but may continue f long time if the case has become one of secondary sepsis One attack usu confers immunity for life but rare second and even third attacks are record.

During War II, van Rooyen and Illingworth (1944) became convinced fr their considerable experience with smallpox in the Middle East that ea diagnosis is much facilitated by the employment of a laboratory test in wh skin scrapings are searched for what are known as variola "element bodies." In eighty cases ranging in severity from mild to fatal hemorrha forms the laboratory and clinical findings corresponded in seventy-seven stances (*i.e.*, 96 per cent). The elementary bodies were said to have be demonstrated with ease in the papular and vesicular stages but they tend to disappear after the onset of pustulation. In no instance in this series di positive laboratory verdict disagree with the final clinical diagnosis of t case, but negative laboratory findings were returned in three cases which prov clinically to be smallpox. Van Rooyen and Illingworth found that the test w not applicable to the diagnosis of chickenpox.

THERAPY

Symptomatic Therapy. In the initial febrile stage of the disease only sym [illegible] ould [illegible] relie [illegible] grai (0.6 gm) every three or four hours, phenacetin, in the same dose and at th same intervals, or amidopyrine in a dose of 5 grains (0.3 gm.) (see und Agranulocytosis for toxic action of this drug). Sometimes these milder agen will not suffice, and morphine or dilaudid must be given. The vomiting is pe haps best controlled by gastric lavage with 1 per cent sodium bicarbona solution; it has been said that the slow intravenous injection of dextrose solu tion will sometimes stop it also. Boeck (1946), discussing experience in Kore after the close of War II, said that in all severe cases partial or total substitu tion of intravenous infusions for food was necessary, dextrose and saline bein given with the daily addition of 200 mg. of ascorbic acid and 20 mg. of thia mine hydrochloride

The severe itching that often occurs is much relieved by the following lotion which has the objection, however, that it dries into a thin crust that ma aggravate the condition unless it is frequently washed off with olive oil, no with water.

Phenol	℥ss	2 0
Prepared calamine	℥iiss	10 0
Zinc oxide	℥iiss	10 0
Glycerin	♏xl	2 4
Solution of calcium hydroxide to make	℥iv	120 0

Twenty per cent argyrol solution should be dropped into the eyes twice daily from the beginning, and one should be especially attentive to the possibility of scarring from conjunctival lesions if the face is so much swollen as to close the eyes Haughton (1942) recommended instead of argyrol for the eyes that one wash them often with boric acid or saline solution, apply drops of 1:1000 acriflavine three times daily, and at bedtime without fail introduce

trength yellow oxide of mercury ointment. Sen (1945) stated the belief the eye complications can be prevented or at least controlled by the ne administration of the sulfonamides and vitamin A.

ilkinson (1943) wrote in rather general terms of the promising results ined with convalescent serum. The serum was obtained from patients who had smallpox for at least thirty days, no evidence was cited as proof of his tention however. Illingworth and Oliver (1944) gave convalescent serum three patients expected to have a severe attack and they all died. Boeck 946) said that convalescent whole blood was used in two of his cases and that one it may have played a part in the recovery

Minimizing Scarring.—If scratching were the chief factor in scarring then it ould seem that children should be the most afflicted in this regard, the fact s, however, that the cosmetic result is very much better in children than in adults. Scratching is of course to be resisted as much as possible for it certainly increases the liability to secondary infection. It has long been held that painting the individual lesions with diluted tincture of iodine or with 5 per cent potassium permanganate solution several times daily will promote healing and minimize scarring, but I have never seen a report of a real study of this procedure. However, Gordon (1947) says that during an outbreak of severe smallpox in the Sudan many years ago it was shown that compresses soaked in potassium permanganate solution and applied to the skin lesions were amazingly successful not only in combatting secondary infection but apparently also in ameliorating to some extent the course of the smallpox itself. In a small family outbreak, McCammon (1939) treated four of his patients with sulfanilamide and three without, the untreated patients all developed the typical eruption, but in three of the treated patients there was only an evanescent macular eruption that rapidly disappeared, and in the remaining patient only three pustules developed McCammon said that those who received sulfanilamide were back at work about a week sooner than those who did not. Patel and Naidu (1940), of India, and Wilkinson (1942), of Hong Kong, found that in the septic pustular stage the sulfonamides undoubtedly diminished fever and reduced complications and also effected a considerable reduction in the mortality rate However, Illingworth and Oliver (1944) gave sulfonamides to most of their 100 patients and felt that these drugs influenced neither the course of the disease nor the extent of the scarring, indeed, they cultured the contents of unbroken pustules in fifteen cases, and since every culture was sterile they found it difficult to understand how sulfonamides could be expected to be of value in reducing scars Jeans *et al* (1944) treated four patients with severe confluent smallpox with penicillin at the height of the eruption; three of the patients survived, including one who had never been vaccinated. In Boeck's [illegible] of cases in the Army at the close of War II, penicillin was given [illegible] infection as soon as the vesicles developed; it [illegible] therapy. Haughton (1942), who [illegible] dia, stated that [illegible] nts suppuration [illegible] duces mortality [illegible] ease. Haughton's [illegible] xylol taken internally [illegible] to a minimum, [illegible] and reduces scarring to a minimum, [illegible] be begun very early in [illegible] but that its employment *must* be begun very early in [illegible] four times a day in mil[illegible] xylol dosage for an adult man was 30 minims (2 cc.) four times a day for three days, then thrice daily for three days, then twice daily for three day[s] and then stopped, the dose was reduced to 20 minims (1.2 cc.) for women, 10 minims (0 6 cc.) for children and 5 minims (0 3 cc.) for infants. This age[...]

is a second rise in temperature which coincides with the pustular stage of the eruption. This second period of fever terminates with the beginning of desiccation, about the twelfth day of the eruption, but may continue for a long time if the case has become one of secondary sepsis. One attack usually confers immunity for life but rare second and even third attacks are on record.

During War II, van Rooyen and Illingworth (1944) became convinced from their considerable experience with smallpox in the Middle East that early diagnosis is much facilitated by the employment of a laboratory test in which skin scrapings are searched for what are known as variola "elementary bodies." In eighty cases ranging in severity from mild to fatal hemorrhagic forms the laboratory and clinical findings corresponded in seventy-seven instances (*i.e.*, 96 per cent). The elementary bodies were said to have been demonstrated with ease in the papular and vesicular stages but they tended to disappear after the onset of pustulation. In no instance in this series did a positive laboratory verdict disagree with the final clinical diagnosis of the [illegible] in three cases which proved [illegible] th found that the test was [illegible]

THERAPY

[illegible] the disease only symp- [illegible]

(0 6 gm.) every three or four hours, phenacetin, in the same dose and at the same intervals, or amidopyrine in a dose of 5 grains (0.3 gm.) (see under *Agranulocytosis for toxic action of this drug*) *Sometimes these* milder agents will not suffice, and morphine or dilaudid must be given. The vomiting is perhaps best controlled by *gastric* lavage with 1 per cent sodium bicarbonate [illegible] intravenous injection of dextrose solu- [illegible] experience in Korea [illegible] tial or total substitu- [illegible] infusions for food was necessary, dextrose and saline being [illegible]) mg. of ascorbic acid and 20 mg. of thia- [illegible]

The severe itching that often occurs is much relieved by the following lotion, which has the objection, however, that it dries into a thin crust that may aggravate the condition unless it is frequently washed off with *olive oil, not* with water.

Phenol	ʒss	2 0
Prepared calamine	ʒiiss	10 0
Zinc oxide	ʒiiss	10 0
Glycerin	♏xl	2 4
Solution of calcium hydroxide to make	℥iv	120 0

Twenty per cent argyrol solution should be dropped into the eyes twice daily from the beginning, *and one should* be especially attentive to the possibility of scarring from conjunctival lesions if the face is so much swollen as to close the eyes. *Haughton* (1942) recommended instead of argyrol for the eyes that one wash them often with boric acid or saline solution, apply drops of 1:1000 acriflavine three times daily, and at bedtime without fail introduce

outer aspect of left thigh, two thirds of the way from knee to hip. It is worth noting that leg vaccinations are more likely to cause large scars than arm vaccinations and that primary leg vaccination in adults may be accompanied by purplish discoloration and cause temporary disability.

and there is a turbid, whitish vesicle, which may or may not become a pustule before it dries and promptly heals All three of these reactions are "takes" because they indicate the degree of immunity and raise it again to maximum Leake, of the U.S.P.H.S., said that all other results indicate deficient vaccine if the technic was proper and the individual in good health.

Complications.—(1) Excessive swelling, abscess formation and lymphatic enlargement indicate secondary infection. Cleanse the pustule with ether and paint with mercurochrome or gentian violet or metaphen solution. Abscesses to be treated surgically with wet dressings. (2) Generalized vaccinia; rare. Pustules around lesion or scattered papules and vesicles over body. Usually only slight fever and prostration. Prognosis excellent and recovery rapid. (3) Autovaccination, caused by failure to wipe off excess of vaccine, the child's finger carrying it to other parts of the body, or child scratches the uncovered pustule. New pustules will be similar to original and are cause for no concern unless involving eyelid or cornea—which calls for ophthalmologic consultation at once (4) After about 500,000 vaccinations in the summer of 1942 at Glasgow, a report was made by Bloch (1942) of 123 regional or generalized postvaccinal rashes, the majority of which appeared seven to eleven days after well-marked positive primary vaccinations in children. A regional papular eczema erupted seven weeks after vaccination of an infant. Diagnostic difficulty was at first considerable but soon diminished except in some cases of papular urticaria Of ninety-eight erythematous or urticarial eruptions, thirty-seven were papular urticaria and twenty pleo-

hy breast-fed boy

eight weeks died

of illness or fifth

day of the complicating eruption; the complicating disease was regarded as staphylococcal. Davidson and Davis (1943), reporting on findings during the same period of mass vaccinating in Scotland, listed four patients ranging in age from four to forty years who developed abnormal reactions eight to ten days after vaccination. Purpuric manifestations appeared in three of the patients, two of whom developed well-marked edema at the same time; the remaining patient showed generalized vaccinia. It was believed that these abnormal reactions might have been related to an allergic tendency,

had cropped up a number of times before in the literature of smallpox and very probably has value.

Removal of Scars.—The use of trichloracetic acid was said many years ago to be sometimes successful in removing smallpox scars (Wise, 1920). Fisher (1938) reported the removal of an accidental (autovaccination) scar by the use of blistering doses of ultraviolet rays.

PROPHYLAXIS

It is said that the Chinese have for many centuries practiced a crude kind of vaccination by thrusting human smallpox scabs up the nose. The Turks had refined upon this somewhat in that they introduced some of the pus from such a scab into a small incised wound of the arm; after an incubation period of a week or so the patient experienced a mild attack of the disease and was then immune. This was the practice that Lady Montagu brought home to England in 1727, where, after some preliminary opposition, it was much used until supplanted by the Jenner method; it also had considerable vogue in the American Colonies—Krafka says that general inoculation of the army occurred during the Revolution. However, by all accounts these induced cases were by no means invariably mild, and Schamberg says that the custom never injoyed much popularity on the Continent. Jenner, in England, conferred upon the world the great boon of vaccination with the virus of cowpox in 1798. In recent times the use of cowpox virus has been given up in favor of vaccinia virus, which is virus originally of human origin passaged through calves; Horgan and Haseeb (1945) showed that the many different strains of vaccinia virus in use throughout the world are immunologically identical regardless of source.

Preservation of Vaccine.—Leake (1943) emphasized the fact that proper refrigeration is of the utmost importance in the preservation of smallpox vaccine; he stated that the vaccine should be shipped by the manufacturers packed in dry ice and that it should be kept in the freezing compartment of the refrigerator. It would seem that smallpox vaccine cannot reasonably be expected to maintain full potency even under proper conditions of storage for more than three months. Trommer (1943) advised that when performing mass vaccinations in a clinic during an epidemic it is advisable to wear rubber gloves in order to avoid acquiring undesirable vaccinations on one's own person (as he did on both thumbs!).

Method of Vaccination.—The instructions given to the Army (Bull. U.S. Army Med. Dept., 6, 651, 1946) were as follows: "Prior to application of vaccine the arm should be washed with soap and water and thoroughly dried. Ether or acetone may be applied to the area but it must be allowed to dry completely before the vaccine is deposited on the skin. Alcohol or other skin antiseptics should never be used in the preparation of the vaccination site as they tend to inactivate the virus and reduce the probability of a successful vaccination. To accomplish the vaccination procedure the multiple pressure method should be used. The needle is held essentially parallel to the skin and the side of the needle point is pressed through the drop of the vaccine and into the skin about thirty times. No blood should be drawn. The common error is to hold the needle perpendicular to the skin rather than horizontal and the point then applied direct, thus making multiple 'punctures' rather than multiple pressures. It is the multiple pressure and not the multiple puncture method which is now accepted as the most satisfactory for the

likely is that during the vaccination reaction the allergic symptoms may recede as they often do in the presence of intercurrent disturbances.

Lapse of Time from Vaccination to Protection.—Successful vaccination performed on the day of exposure will almost always completely protect; performed up to a few days before onset of the disease it will at least make the attack milder.

It is roughly true that the individual is protected completely twelve days after performance of vaccination, but since the vaccination may not "take" the first time it is tried, it may be wise to vaccinate twice if an individual presents himself within four days of the time of known exposure, the second time two days after the first and 2 inches removed from it.

Duration of Immunity.—It is estimated that protection in white persons lasts from seven to ten years and in the Negro four years, but this is largely a [illegible]

often interpreted as evidence of retained immunity, whereas we know that this only indicates unsuccessful vaccination. The authoritative study of Dearing and Rosenau (1934), on medical students at Harvard, indicated that the immunity conferred by a single vaccination lasts twenty years or more in most individuals, welcome news, but since one of the twenty-two students revaccinated less than five years after the first successful vaccination gave a primary "take" (evidence of complete loss of immunity), we are not helped much in determining the absolute minimum duration of protection. But it may be that infection with smallpox is more difficult after successful vaccination with vaccinia virus than is reinfection with vaccinia virus on revaccination. Cole- [illegible]

though upon immediate revaccination of the entire unit of 938 men upon the diagnosis of this case, 5 per cent of them developed "takes" though all of them had been previously vaccinated within a five-year period.

When and How Often to Vaccinate.—In view of what has just been said above, it is apparent that we have no absolute guide. The following seems to be reasonable. Children should be vaccinated after three months and not later than one year of age, again on entering school, and again at puberty, all children and all adults should be revaccinated when there has been a known exposure, when an epidemic threatens, or upon visiting a region where foci of [illegible]

but it does not seem to me that a very clear case was made out for this hypothesis. Herbut (1944) reported a fatal case of diffuse glomerulonephritis following revaccination after thirty years and felt that the cause was sensitivity to the protein of vaccine virus although he recognized that sensitivity to calf serum itself could not be absolutely ruled out. (5) The British statistical study of 1931 revealed that for each million persons vaccinated for the first time there are nineteen disorders of the nervous system, with six or seven deaths, and for each million persons revaccinated there is one such disorder, with a fatal issue. The report of Anderson and McKenzie (1942), following the vaccination of about 500,000 persons in Glasgow, very well confirmed the above findings since there occurred in this group seven cases of postvaccinal encephalomyelitis with two deaths; six of the seven cases were in persons over five years of age vaccinated for the first time. Clearly, there is no cause for anxiety here. Since the great majority of the cases occur in children primarily vaccinated between the ages of three and thirteen, the well-established precept of vaccinating in early infancy is roundly confirmed. Jorge's (1932) study of these postvaccinal nervous disorders was most exhaustive. It is probable that little if any risk attaches to the revaccination of a person who has suffered postvaccinal encephalitis years before.

How Long to Continue Trying if No "Take" is Obtained?—Failure to obtain one of the three kinds of reaction described above under "successful 'take,'" does not indicate immunity b... Repeat at two-week intervals until a "take ... attempts before success was attained ... tain a "take" are due to ignorance of the facts regarding storage of the vaccine

Best Time of Year.—Hot months predispose to infection because of perspiration ... there are the respiratory infec... ation This ... not of much importance.

Contraindications.—Women may be vaccinated at any time during pregnancy without fear of obstetrical complications, but successful vaccination of the mother does not convey specific immunity to the infant. It is best not to vaccinate during menstruation. Eczema, impetigo, furunculosis or other "open" skin diseases or fissures, ulcers, burns, or wounds should cause postponement unless there is an epidemic; likewise gastro-intestinal upsets or malnutrition. Acute infectious diseases may cause delayed or atypical "take" but are not in themselves contraindications in case of possible exposure; however, Stitt (1943) cited the case of a child whose symptoms of postinfectious encephalomyelitis following measles were just beginning to subside when he was vaccinated for smallpox and in whom there occurred a marked increase in ... the vaccination. Lymphom... be made worse. ... ay be performed ... but in tuberculous children, and in ... fortunate ..., with his easy infection by pyogenic bacteria, should perhaps be vaccinated only during ... in asthmatics or other aller... local and ... is more

previously during the epidemic in Japan and Korea just following the close of the War, thus emphasizing the fact that comparatively recent vaccination is required to protect fully against the severe form of smallpox. Innes (1946) wrote of a population of some 500 Europeans living in an Indian industrial town where smallpox is very common; it is the practice annually to revaccinate the whole population at risk and none of these people develop the disease even in modified form. Innes recognized of course that it would not be [illegible]

[illegible] nection with localized outbreaks of severe smallpox resulting from imported cases following repatriation after War II, it was rediscovered that a well vaccinated person after contact with a case of smallpox may develop a relatively mild attack of the disease with the eruption so sparse and modified that the correct diagnosis is excusably missed; the mildness of the illness in these individuals usually causes them to impose no restriction on their activities and therefore they very probably initiate severe cases in wholly unprotected persons. Universal vaccination is the only real protection against smallpox.

STREPTOCOCCAL SORE THROAT

(Epidemic Sore Throat, Septic Sore Throat)

The symptoms in this frequently seen type of sore throat are sudden onset of chilliness, malaise, headache and vague body pains, high rise of temperature and swelling of the cervical lymphatic glands The pharynx is extremely painful, swollen, congested, and usually shows a diffuse, thin grayish exudate; sometimes there is a punctate rash on the palate; occasionally the larynx is chiefly affected. The complications are those also most frequently seen in scarlet fever, *i.e.*, peritonsillar and retropharyngeal abscess, cellulitis of the neck, tonsillitis, otitis media and mastoiditis, kidney and joint involvements: indeed, it is nowadays accepted by most observers that streptococcal sore throat and full-blown scarlet fever are very closely related entities The disease frequently occurs in [illegible] epidemics in the winter and spring, *often directly traceable to t*[illegible] in a [illegible] number of such epidemics in [illegible] the individual outbreaks as scarlet fever or septic sore throat depending *upon* the frequency of typical scarlatinal rashes. Oftentimes the patient with streptococcal sore throat will remain in a state of near prostration for some time following the few days of acute symptoms; a recurrence several days after resuming activity is not uncommon. Swift (1947) expresses the consensus of many [illegible] fever, [illegible] e dur- [illegible] infec- [illegible] d the tions, the subsequent and often asymptomatic [illegible] final picture of cardiac failure, so many events have intervened and so many [illegible]

Dingle *et al.* (1947), of the Commission on Acute [illegible]

have asked for greater recognition of the fact that not all cases of exudative tonsillitis and pharyngitis are due to hemolytic streptococci, pointing out that the non-streptococcic type of the infection is a benign disease without recognized complications. However, since most of the cases of the latter sort are undoubtedly seen in the home and not the hospital and their differentiation from the streptococcal cases is difficult in the beginning without the aid of cultural and serologic studies, it would seem to me that the general practitioner's intelligent management of the cases would be to treat them all upon the assumption of a streptococcic etiology.

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Penicillin is controlling these infections as no other agent ever has. Davison (1946) found that in all but two of his twenty-eight patients the clinical response to full parenteral therapy was excellent; he felt that it should be rare to require more than three days of treatment. Plummer *et al.* (1945), in a series of the same size, found their patients usually free from symptoms in twenty-four hours, but they also observed that the organisms were again recoverable from the throat and the symptoms often returned unless the therapy was continued for six days. Woodward and Holt (1945) obtained improvement in forty-eight hours in twenty-seven of thirty-one patients with both lozenges and the spray of penicillin. It is strange to find Rantz *et al.* (1947) of the opinion that penicillin is of no direct value.

The sulfonamides have not been successful in the treatment of streptococcal sore throat. The most thorough study I have seen was that of the Commission on Acute Respiratory Diseases (Dingle *et al.*, 1945), who treated alternate patients in a series of 100 with sulfadiazine, their conclusion was that from the standpoint of practical therapeutics no worthwhile advancement was derived from the use of the drug.

The patient oftentimes experiences some relief, probably entirely psychic, from gargling with Dobell's solution (Compound Solution of Sodium Borate, N.F.) diluted one-half with water, or from using as gargle or spray the Alkaline Aromatic Solution, N.F. Cold packs about the throat often give much relief. Suppurative complications in the neck require surgical treatment.

SYPHILIS

Syphilis is a venereal and general constitutional disease, caused by *Treponema pallidum.* Whether or not it was unknown in the civilized world prior [illegible]

[illegible]

from her analysis of the results of blood tests made during the examination of men for the draft that in no section of the country was there any great

rise in the incidence of syphilis; indeed for the country as a whole there was if anything a decrease in the number of syphilis cases detected. The long-term decline in the death rate from syphilis in our country represents especially the experience among white persons, but in recent years substantial progress is also being made in reducing the mortality among Negroes, who constitute the great reservoir of the disease. Incidence has usually been found to be high in such primitive races as have been investigated from this standpoint; for example, a 50 per cent infection rate based upon clinical observations only has been determined in certain nomadic tribes of eastern Siberia. Of very great interest is the disease bejel, which is alleged to exist as a completely nonvenereal contagious disease of children in the Bedouin population in the valley of the middle Euphrates River. However, some observers are doubtful of the nonvenereal character of bejel, some look upon it and yaws as the same thing, and others consider that bejel may be a disease intermediate between yaws and syphilis. The earlier belief that classical neurosyphilis does not occur among primitive peoples in whom primary syphilis is untreated is now entirely discredited; that its rarity in certain regions despite a high incidence of syphilitic infection *per se* may be due to the endemicity o ... Needles (1935) ... by

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nonvenereal type of spirochetosis whose distribution is limited almost exclusively to the dark races, as identical with syphilis; Lieberthal (1943) described the first three cases of this malady in the continental United States

In the vast majority of instances syphilis is acquired by sexual intercourse ... penicillin a variety ... syphilis," is being ... ted and cured and is then reinfected by the wife; she is treated and cured and then reinfected by the husband. However, Beerman (1946), having thoughtfully reviewed the matter, has authoritatively stated that the data on reinoculation of human beings with syphilis are not of sufficient size to answer definitely the question whether reinfection is possil ... of non-sexual transmission is higher than generall ... of 971 cases of syphilis diagnosed in ... York Department of Health, 5.7 per cent were found to be extragenital. The seriousness of early unsuspected syphilis of this type is evidenced in such reports as that of Rowntree and Hendon (1940), who found extragenital transmission of the disease among five persons in one family. Ingraham and ... of syphilis from a mother to her ... ther by contamination ... at the question of the ... who themselves have ... lis) is still debatable, though they reported one such probable case themselves.

In the classical case of syphilis, venereally acquired, the course is generally the following: (a) The appearance of the primary sore (chancre), which is multiple in about 25 per cent of cases, after an average incubation period of twelve to forty days. (b) The appearance of secondary symptoms at an average time of eight weeks after the appearance of the chancre: skin rashes of such varied sorts as to make description impossible here; mucous patches

in the mouth or anal region, plus the symptoms which often accompany general infections in greater or less degree, such as malaise, fever, anorexia, sore throat, headache and joint pains and nervous manifestations; very rarely acute meningitis or acute nephritis or nephrosis. (c) A so-called "latent period" during which the infection is apparently quiescent for a variable term of years (d) The appearance of the "tertiary" period of the disease, which is characterized by protean and serious symptoms due to gummatous or diffuse lesions anywhere in the body.

The above classification into primary, secondary, latent and tertiary stages is largely arbitrary and is by no means clearly demarcated in all cases. In congenital syphilis the fetus is infected *in utero* by the mother, who must herself be first infected Rose *et al.* (1946) have recently reemphasized the fact that

intense and serious because of interference in the rapid growth of tissues in the developing child, other important differences are the immunologic immaturity of the fetus and the tendency to debility and secondary infection. The most acute stages of congenital syphilis and the highest mortality are en-

about 20 per cent

tions: yaws, bejel, pinta, kala-azar, relapsing fever, ratbite fever, filariasis, malaria, infectious mononucleosis, a smallpox "take," lymphogranuloma venereum, atypical pneumonia, measles, leprosy, giving of a "booster" dose of

throughout life Talmage *et al.* (1946) found the incidence of false-positive reactions very high in battle casualties during War II, running as high as 55 per cent in fracture cases, however, most of these doubtful reactions were in the low range Boerner *et al.* (1946), studying the matter for the Red Cross Donor Centers during War II, failed to find statistically valid data supporting the hypothesis that successive bleedings are capable of producing false-positive reactions. It is said that Neurath's technic is helpful in the differentiation of false and true positive tests. Becker (1947) says he believes that Kahn's verification reactions are of assistance but that they certainly cannot be recommended to the nonsyphilologist. Kampmeier says that in primary syphilis by the time the chancre has been present for two weeks positive complement-

fixation and precipitation blood tests will be obtainable in well over half the patients, though in rare instances the blood may remain seronegative as long as two months after the appearance of the lesion; secondary syphilis is accompanied by positive tests in 100 per cent of cases; late benign lesions show positive tests in 95 per cent or more of cases; negative tests are encountered ... per cent of cases; most forms of ... tests, but they may be negative ... out a third of the cases of tabes dorsalis when the physician is first consulted; in untreated latent syphilis with the passage of years either the complement-fixation or flocculation tests or both may become doubtful or negative. The dilemma in interpretation of a positive reaction is posed when there is no history of syphilis or of previous antisyphilitic treatment, a negative physical examination and a negative ... examinations, and no ... eaction Kampmeier ... ersity Hospital their ... (a) persistently and ... tion and flocculation ... (b) persistently and repeatedly positive flocculation tests with doubtful complement-fixation tests are considered to mean syphilis especially in the presence of admitted and repeated sexual exposures; (c) persistently and repeatedly positive flocculation ... fixation tests are accepted as indicating ... years, since par- ... age of a decade ... tion and ...

test cannot be accepted to mean syphilis.

TREATMENT OF EARLY SYPHILIS

The Superiority of Penicillin.—There can no longer be any reasonable basis for doubt that when penicillin is properly administered it will cure the ... of patients with primary and secondary syphilis. *It is as active* ... sults with it are ... arseno-bismuth methods that were tried during War II. Of course the practical non-toxicity of penicillin as compared with intensive metal therapy is too well known to ... If then one is to compare penicillin alone ... e only to compare it with ... which the patient experi- ... l. *However, in this older* ... *was high, a patient com-* ... *in clinic practice, he* ... *l he* ... *l to* ... *with* *15 per cent of instances, both of these latter depending on* ... advantage of penicillin is ... omplete ... type of ... at this

might be an advantage over penicillin, for when the latter agent is used the patient is merely "looked at" at each of the follow-up visits and nothing is

in those days, we would have lost from the Clinic a fourth of the patients that we did.

Penicillin was adopted as the drug of choice in our Army in the European theater of operations on June 26, 1944, a unit dose of 40,000 being given at three-hour intervals night and day for seven and a half days to give a total

the 517 patients with seronegative primary syphilis who had been observed for more than nine months, 94 3 per cent were progressing satisfactorily at

Of the 462 patients with seropositive primary syphilis who were followed for more than nine months, 89 9 per cent were progressing satisfactorily at the time of their last observation, 10 1 per cent being declared unsatisfactory because of infectious relapse in twenty, serologic relapse in fourteen, abnormal cerebrospinal fluid in two and serum fastness in twenty-two (the results for one patient were entered as failure twice because of concomitant

who were followed for more than nine months, 83 0 per cent were making satisfactory progress and 17.0 per cent unsatisfactory progress at the time of last observation, the latter including four patients with infectious relapse, six with serologic relapse, twenty-seven with serum fastness, and three with abnormal cerebrospinal fluid. Among the 120 patients in this group whose cerebrospinal fluids were examined only three were found to be abnormal It is to be noted that in only five of 719 fluids examined in all the groups was any abnormality noted, two of these instances being in cases of seropositive primary syphilis and three in cases of secondary syphilis. This low incidence of asymptomatic neurosyphilis in penicillin-treated patients has also been independently remarked by O'Leary (1947) Summarizing Sternberg and Leifer's study one can say that of the 1400 patients 90 6 per cent were progressing satisfactorily and 9 4 per cent unsatisfactorily when the final observations were made. The variation in response of the three phases

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of

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Army patients were in the seronegative primary stage than is usually the case in civilian clinics. Sternberg and Leifer pointed to the possibility that some of their infectious relapses may well have been reinfections, and Morrow (1947), in discussing their paper, stated his certain belief that they were

reinfections since all the patients had solitary darkfield positive lesions an were seronegative. Morrow pointed out that when relapse follows treatment the serologic reaction drops in titer, though rarely to negativity, and then rises during the next four to eight weeks when lesions appear, and that when this happens the lesions are usually multiple papules. Syphilologists are beginning to concede that probably under penicillin we are going to see a great many true reinfections classified as infectious relapses, of course if this is true then the efficacy of penicillin is actually higher than we at present assume it to be on the basis of the actual data at hand, since in most instances in those data the clinical evidences of failure have been based upon the occurrence of "infectious relapse." Rein (1947) has pointed out, on the basis of his extensive experience in the Division of Serology at the Army Medical Center, that if penicillin-treated patients are subjected to serologic examinations at weekly or monthly intervals it is possible, through observation of an increase in serologic reaction, to predict a relapse about one month before there is any clinical evidence of the same—obviously, therefore, the patient should be impressed with the importance of reporting to his physician for serologic and clinical examinations at monthly intervals for at least one year following the completion of penicillin therapy.

Although penicillin does not appear in the cerebrospinal fluid when it is given intramuscularly it seems undoubtedly effective in the treatment of acute syphilitic meningitis when given by this route. Nelson and Duncan (1945) reported ten cases of acute syphilitic meningitis in which the immediate results were excellent both from a clinical and a laboratory standpoint; after one year nine of the patients remained clinically well so far as neurologic evidence of syphilis was concerned, six had attained seronegativity of the blood, and all ten had completely normal spinal fluid examinations It was believed that these results were superior to those obtainable with metal chemotherapy. One of the patients had developed an infectious mucocutaneous relapse but this patient had been given only 600,000 units of penicillin at the initial treatment.

Schedule for Employing Penicillin Alone.—Reynolds (1946), of the Venereal Disease Division of the Medical Clinic at Johns Hopkins Hospital, reviewing the experience of the Committee on Medical Research in the penicillin treatment of approximately 35,000 patients, felt it possible to outline in general terms the use of penicillin in the treatment of early syphilis, emphasizing the fact that his interpretation was personal. He said it is most convenient to start with an arbitrarily selected total penicillin dosage, which for seronegative primary syphilis should be a minimum of 3,000,000 units, for seropositive prima [illegible] for secondary syphilis not less than [illegible] the drug in aqueous solution the [illegible] n injections of 50,000 units at intervals of three hours for seven and one-half days in seronegative primary syphilis, for twelve and one-half days in seropositive primary syphilis, and for seventeen and one-half days in secondary syphilis If the penicillin is given in peanut oil and beeswax (Romansky formula) he felt that single daily intramuscular injections should be given for ten days in seronegative primary cases, for seventeen days in seropositive primary cases and for twenty-three days in secondary cases. Romansky and Rein (1946), at the Walter Reed General Hospital, reported the satisfactory employment of a single daily intramuscular injection of 300,000 units in

peanut oil and beeswax; Kulchar (1946) reported that similar findings had been made in San Francisco, and Sternberg (1946) said that in two other

in aqueous solution. Thomas *et al.* (1947), reporting from the Rapid Treatment Center in Bellevue Hospital, found a single daily injection for eight *days of 600,000 units in peanut oil and beeswax "unusually" satisfactory in* their 802 patients. Reynolds (1947) also favors the larger dosage and, as already pointed out, a longer period of administration, but he feels that when using this type of preparation occasional twenty-four hour lapses in

ment of arsenic. Reynolds (1947) felt that its inclusion is still largely a matter of personal preference, not because the evidence of its superiority, particu*larly in seropositive primary and secondary cases, is not ample,* but because it is recognized that the administration of arsenicals introduces a risk of

experimental *evidence* indicating that the intramuscular administration *of*

relapsing cases.

Schedule Employing Penicillin and Bismuth.—The program of the State Cooperating Venereal Disease Clinics of the Massachusetts Department of

units) in the seven and a half days with bismuth given again precisely as in the first course. The reactions to bismuth are mild and infrequent compared to those provoked by arsenic.

Schedule Employing Penicillin and Both Arsenic and Bismuth.—Eagle *et al.* (1946) have shown in the experimental laboratory that mapharsen and penicillin act synergistically when administered concomitantly, *i.e.*, the total effect is greater than would be expected from mere addition of the individual effects of the two agents; these findings have been confirmed in the clinic

injections of mapharsen in a dosage of 40 mg. per injection are given on four consecutive days; (b) on the fifth day penicillin treatment is begun at the rate of 40,000 units intramuscularly every three hours for seven and a half days for a total of 2,400,000 units; (c) on the last day of the course of penicillin, treatment with bismuth subsalicylate in dosage of 1½ grains (0.1 gm.) is started, ten intramuscular injections being given at the rate of one every fifth day. O'Leary and Kierland adopted this program because it employs arsenic in sufficiently few injections and small dosage to avoid a high incidence of severe complications and because the ten injections of bismuth given after the penicillin permit continued observation of the patient as well as adding materially to the therapeutic effect. However, the eleven and a half days of hospitalization and the total extension of the treatment over a period of about two months make it not an ideal schedule from the economic and technical standpoints, though O'Leary and Kierland felt that if further trials with the Romansky formula proved it to be satisfactory (as they seem to have done) its incorporation into some such system as theirs would obviate the need for hospitalization O'Leary (1946) says of this method of treatment that if a clinical relapse does not occur during the first three months after completion of the course, and if the reaction to serologic tests and the titer of the syphilitic amboceptor show evidence of reduction, the course of treatment is not repeated but the patient is kept under observation; if, on the other hand, a clinical relapse occurs, and if the reaction to serologic tests and the titer of the syphilitic amboceptor are first reduced but later increased, the course of treatment is repeated

... above ... he ... ose ... om ... d-

penicillin to a twenty-six week schedule ... ule is outlined in Table 4.

Mapharsen may be injected as rapidly as one wishes; indeed, from the standpoint of preventing pain from venous spasm, the faster the better. Since ... of the solution

... efficacy ... use. Of ... parable ... ocymol, ... uth and bismuth ethyl camphorate, bismosol, bismuth sodium ... potassium tartrate, thio-bismol, iodobismitol with benzocaine. However, the water soluble preparations oftentimes cause considerable pain upon injection

and they must be given two or three times weekly; some of the liposoluble preparations must be injected twice weekly also. Sobisminol mass, which may be taken by mouth, has not been very much employed; in Barnett and Meininger's (1945) series of patients about one-third had gastro-intestinal disturbances and in 6 per cent of the cases these were severe enough to necessitate discontinuance of treatment. The most serious objection to sobisminol mass,

TABLE 4.—TWENTY-SIX WEEKS ARSENO-BISMUTH THERAPY

	Week	
Mapharsen, 60 mg., intravenously twice weekly, total 20 injections	1, 2, 3, 4, 5	Bismuth subsalicylate, 0.2 gm., intramuscularly once weekly, 5 doses
	6, 7, 8, 9, 10	Omit bismuth for 5 weeks
Omit mapharsen for 6 weeks	11, 12, 13, 14, 15, 16	Bismuth subsalicylate, 0.2 gm., intramuscularly once weekly, 6 doses
Mapharsen as in first course, twice weekly, total 20 injections	17, 18, 19, 20, 21	Omit bismuth for 5 weeks
	22, 23, 24, 25, 26	Bismuth subsalicylate, 0.2 gm., intramuscularly once weekly, 5 doses

Results.—According to Sternberg and Leifer (1947), this twenty-six weeks

were all healthy males between eighteen and thirty-eight years of age and living a well-regulated life and generally in an excellent state of nutrition. In general *this treatment was tolerated* very well, for in only two instances in the 3000 cases was it necessary to abandon arsenical therapy, in one case because of severe jaundice and in the other an arsenical dermatitis. There were sixty-one other patients who were forced by reactions into variable periods of interruption but they were all able to complete the treatment within thirty-eight instead of twenty-six weeks. There were no deaths from treatment in these 3000 patients, but an approximation of the probable mortality rate from the twenty-six weeks treatment may be obtained, in the opinion of Sternberg and [illegible]

mapharsen some years ago, says that *at the conclusion of the twenty-six weeks* of treatment (with which he combines penicillin in dosage of 2,400,000 units during the first eight days) the patient is kept under observation and a Wassermann *taken once a month for the first two months or longer if the reaction is* still positive; if the reaction is negative the examination is at two-month intervals until a year has elapsed from the onset of the treatment; then a spinal *fluid* examination is made and if this and the serology are negative the *patient* is discharged to biyearly examination with instructions to report immediately for examination if any skin lesions develop.

Reactions to the Specific Drugs.—These are considered at the end of the article on Syphilis.

TREATMENT OF SYPHILIS IN PREGNANCY

In a report on syphilis in pregnancy, prepared for the U.S.P.H.S. in 1940, an authoritative committee made the statement that only 17 per cent of the known conceptions in untreated syphilitic women result in living nonsyphilitic [illegible] stillbirths, or [illegible]

at the fetus *through* the mother. In searching for syphilis in the mother [illegible] should remember that the clinical manifestations of the disease are often suppressed during pregnancy and that blood serologic examination is *therefore most important. But a mere* negative test *very* early in pregnancy, even if coupled with a negative history, may not be sufficient, for syphilis may have been acquired after conception took place and therefore for complete safety *in selected instances it may be necessary to repeat* the test at intervals throughout the period of gestation.

Since it is definitely established that the fetus may be infected any time *after the sixteenth week, the finding of* Woltz and Wiley (1946), of the Philadelphia group, that penicillin is transmitted to the fetus as early as the tenth week of gestation is of very great importance. Furthermore, penicillin may *apparently be used successfully even late in pregnancy* provided the child is still viable. Cole *et al.* (1946) observed that even with *dosage* completely inadequate from the standpoint of treatment of syphilis in the mother the *child* may be born *free from the disease. This should* be contrasted with the feeling of syphilologists in the arseno-bismuth era that treatment instituted after the fourth month of pregnancy might perhaps produce a viable child

but one that still had syphilis. Additional facts that seem to make penicillin particularly suitable for employment in syphilis in pregnancy are: (a) it may be given in a single course over a short period; (b) severe reactions need not be feared; and (c) it is apparently curative of the disease in the mother, at least if she is in an early stage, at the same time that it is preventing transfer of the disease from her to the fetus.

Results of Penicillin Therapy in Early Syphilis.—The studies in Philadelphia of Ingraham, Stokes, Beerman *et al* (1946), and those in Baltimore of Goodwin and Moore (1946), have yielded spectacularly favorable results in the prevention of syphilis in the fetus through treatment of the pregnant mother with penicillin. In studying these combined results it is preferable to limit oneself, as Goodwin and Moore did, to an analysis of the findings in only those cases in which the women were in the primary or secondary stages of the disease, for it is practically certain that the fetus born of such a mother will be syphilitic if untreated though there is not such certainty with regard to infants born of mothers with latent syphilis In the two combined series there were fifty-seven mothers treated, seven of them in primary syphilis and fifty in secondary syphilis. Only two of the total number of patients had had some antisyphilitic therapy prior to entering the study, but one had darkfield positive genital lesions and the other a rising blood serologic titer at the time of instituting the penicillin therapy in this study. Fourteen of the mothers were treated before the sixteenth week of pregnancy, thirty-one between the sixteenth and thirty-second weeks, and twelve in the thirty-second week or later. In five of the fifty-seven patients it was felt advisable to give a second course of penicillin therapy during the pregnancy, in two instances because of failure of immediate serologic response and in the other three instances because of serologic relapses following the initial penicillin course The status of the infants born of these penicillin-treated mothers was as follows at the time of the report of Goodwin and Moore upon the combined series. (a) a total of sixty infants was born to the fifty-seven mothers, three of the mothers having had two pregnancies during the second of which no treatment was given, (b) all sixty infants were born alive and only one developed syphilis (in this case the mother had been given 1,200,000 units of penicillin for secondary syphilis at the fifth month of pregnancy, clinical relapse had occurred at the ninth month of pregnancy, and the infant was born with syphilis), (c) fifteen of the infants were born seroposi tive but reverted to negativity during the first month, two were born serc positive and reverted during the second month, and one was born seropositiv and reverted during the third month, (d) the follow-up period on the infan at the time of the report was as follows eleven were followed for two months, twenty-nine for two to six months, thirteen for six to twelve months, and seven for more than twelve months, (e) during all of this time fifty-nine of the sixty (excluding the one that was born syphilitic) remained clinically, roentgenologically and serologically normal, though one infant died at nineteen weeks of acute nutritional disturbance and sickle-cell anemia.

Comparison with Arseno-Bismuth.—Goodwin and Moore (1946) point out that with the older system of administering metal chemotherapy to the mother even with mapharsen given two or three times weekly during the time between the date of diagnosis and delivery, the best results in the fetus are not obtained unless treatment is started early in pregnancy, *i e*, before the fifth month, and continued throughout the remainder of the gestation Analysis of the reports of Sadusk and Shaffer (1942), Rattner (1943), Neilson *et al.* (1944), Speiser

et al. (1945), and Curtis and Morrow (1946), in which an aggregate of 183 pregnant women with early syphilis were treated intensively with mapharsen, reveals that about 12 per cent of the babies were born with syphilis in spite of treatment. It therefore seems that penicillin is incomparably superior to metal [illegible]

this failure rate of 1.6 per cent would have been reduced to zero had the mother of this one infant been retreated when she relapsed at the ninth month. Furthermore, it seems that with penicillin the results are equally good no matter what the duration of pregnancy at the time of treatment, while with metal therapy they are likely to be very bad if treatment is begun after the fourth month.

Penicillin Dosage Schedule.—Ingraham *et al.* (1946), observing two actual and two threatened abortions in their forty-nine treated women, interpreted this phenomenon as possibly due to Herxheimer reaction and definitely advised reduction of initial penicillin dosage for the first forty-eight hours of treatment; *i.e.*, the eight injections during the first day to be only 10,000 units each, the next eight to be 20,000 units, and the remaining fifty-four to be 40,000 units to make the total of 2,400,000 units. But similar accidents were not observed in the thirty-one cases of early syphilis in pregnant women treated by Goodwin and Moore (1946) or in the 156 treated by Speiser and Thomas (1946). Three of the four actual or threatened abortions in Ingraham's [illegible] Moore point out [illegible] that [illegible] uals

with early than with late syphilis. Goodwin and Moore, therefore, do not believe that abortion, actual or threatened, is a frequent evidence of thera- [illegible] penicillin-treated mothers or that great initial caution in

[illegible] o have [illegible] in the [illegible] f other [illegible] ng than

[illegible] pletion [illegible] quan-

titatively titered serologic tests at least as often as once a month until delivery [illegible] The

[illegible]

logic relapse or the original maternal serologic titer does not [illegible] (1946) make the point [illegible] e it may [illegible] rsistent [illegible] er treat-

ment.

The infant must be followed after birth for a minimum period of three months by means of frequently repeated physical inspections, quantitatively titered blood serologic tests preferably every two weeks, and roentgenograms of the long bones taken preferably at the first and sixth weeks of life. Cole *et al.* (1946) say that a positive reaction to a serologic test for syphilis at birth may

simply mean a reflection of the mother's reaction, but that after the second or third month this is no longer true and that if such a child has not only a positive serologic reaction but also a persistent rise in titer, perhaps along with clinical symptoms, then the problem of retreatment arises

[illegible]

syphilitic woman who has been previously treated with penicillin, and whether or not this earlier treatment was apparently successful as to the mother's infection, to be retreated with penicillin in each succeeding pregnancy.

It seems to be the consensus that an infant may be safely nursed by a mother who is being actively treated at the time, the danger of infection of the infant being not through the ingestion of infected milk, which is unlikely, but with the possibility of the development of relapsing infectious lesions about the nipple

Results of Penicillin Therapy in Latent Syphilis.—Ingraham *et al.* (1946) treated twenty-three pregnant women with latent syphilis (nineteen early—less than four years' duration, three late—more than four years' duration) and one with congenital syphilis The twenty-one children were born alive and all were apparently normal with no examples of congenital syphilis, but since Goodwin and Moore's (1946) analysis of several reports showed that 85 per cent of babies of mothers with latent syphilis are born normal and nonsyphilitic even without any sort of treatment, these results are not so impressive as those in early maternal syphilis and do not constitute as severe a test of penicillin's efficacy.

TREATMENT OF CONGENITAL SYPHILIS

In the arseno-bismuth era the more recent the mother's infection and the less treatment she had had the more likely was the infant to be born with a mucocutaneous, osseous, nephritic, or other severe form of the disease which took it off despite the most heroic chemotherapeutic and feeding efforts to save its life. But nowadays penicillin is so effective in preventing syphilis in the fetus when it is administered to the mother during her pregnancy that such cases will rarely be seen when mothers have availed themselves of prenatal care. But the syphilitic woman who comes to term without having had any professional care at all will of course continue to present the world with syphilitic infants. During the first six months of the lives of these infants the lesions are chiefly ectodermal, mucocutaneous and osseous; from six to eight years they are mostly bony, periosteal and corneal, and at puberty the corneal and nervous lesions are likely to preponderate In the latter two periods keen diagnostic study will often detect the heredosyphilitic even though the signs are not outstanding, but the disease is often extremely resistant to treatment [illegible]

literature caused her to conclude that congenital syphilis produces definite syphilitic interstitial and nodular myocarditis. Undeniably it is in the first age period of congenital syphilis, from birth to perhaps two years, that the best hope of effecting a cure lies.

Penicillin in Early Congenital Syphilis.—The definitive study is that of Platou *et al.* (1947), who brought together all the observations incident to the treatment of 252 infants in five cooperating university clinics. One hundred and thirteen of the infants were under three months of age, sixty-three between three and six months, forty-six between six and twelve months, and thirty-six during the second year of life. A satisfactory outcome was considered the subsidence of observed clinical manifestations in conjunction with negative or progressively declining serologic titer, an unsatisfactory result the persistence of reversible manifestations with an unchanged or rising serologic titer or with relapse. Entirely satisfactory results were achieved in 73 per cent of instances and unsatisfactory in 9.1 per cent; in the remaining 17.9 per cent the results were still classified as uncertain at the time of the report. The age at the [illegible]

orders at the time treatment was begun and early improvement in these cases was encouraging in all but one instance, though it was felt that no more than a tentative statement in this regard could be made. The authors gained the clinical impression that the nutritional status of the patient when treatment was initiated had some prognostic import, though admittedly they were unable to support this hypothesis with statistical data. Clinical relapses occurred in only 2.4 per cent of the total number of cases, relapse occurring as early as three months and as late as eleven months after initial therapy. These relapses were treated with two or more times the original dosage of penicillin and results again became satisfactory in all cases. Over half of the patients experienced no reaction, and none of the reactions was considered severe enough to justify stopping or even modifying the treatment plan. In the total of 252 infants treated there occurred only nine deaths within fourteen days after treatment was started, in regard to syphilis, results in these nine patients had been con- [illegible] ... certain for four

died between fourteen days and one month after treatment was [illegible] results as to syphilis having been considered satisfactory for two, unsatisfactory for one, and uncertain for five. Immediate causes for death other than [illegible] not be examined. Ten [illegible] he effect of [illegible] y for seven with too few observations for proper evaluation of the results in the other three. Causes for death other than syphilis were recognized in all but two; these died at home and reliable information could not be obtained.

Platou *et al* emphasized that a fatality rate of 10.7 per cent from all causes in this series of penicillin-treated infants is slightly lower than that observed among a similar group of infants treated by other plans employing arsenical compounds and heavy metals. Add to this advantage the fact that penicillin

that it may be given in equal intramuscular injections every three hours for a period of fifteen days.

Penicillin in Late Congenital Syphilis.—Hanson (1947), reporting on the treatment of eleven children with interstitial keratitis with penicillin, stated that four appeared to have a favorable clinical response but that in the remaining seven cases either improvement was not noted or the results were difficult

with symmetric hydroarthrosis (Clutton's arthritis), two of the patients did not show any response and the joint effusion remained in the knees for several months after treatment, while in the third improvement seemed to occur but the effusion reappeared in the other knee soon after the patient was discharged from the hospital and a week later interstitial keratitis developed in this patient. In the series of these observers there were also nine patients with inter-

in circumcorneal congestion and immediate clearing of the corneal opacity, but two weeks later the keratitis recurred and involved the other eye, retreatment with penicillin, however, being again effective. In a patient in whom the interstitial keratitis developed after the administration of penicillin for Clutton's arthritis, further penicillin therapy resulted in a slow but satisfactory

(1941) and Corner (1944) reported the successful adjuvant employment of riboflavin in a small number of cases An ophthalmologist should see these cases also, for the proper use of atropine and dionin locally may greatly contribute toward cure.

Yampolsky and Heyman also reported the treatment of six patients with late congenital asymptomatic neurosyphilis, most of the patients having received adequate arseno-bismuth therapy previously with no apparent effect on the spinal fluid observations. The age of these patients at the onset of treatment ranged from ten to twenty-five years and they received a total dosage of

observers, but one patient with mild eighth nerve deafness obtained improvement in hearing after receiving penicillin.

Arseno-Bismuth Therapy.—Conceivably there may arise circumstances in rare instances in which it is necessary to employ arsenic and bismuth instead of penicillin. Cole *et al.* (1940) stated that appropriate mapharsen dosage in

stated on the package) be used per week in combination with arsenic in some such scheme as that in the following chart of Cole *et al.*

Week.	Treatment.	Week.	Treatment.
1 ..	Arsenical in one-third to one-half full dose	29–40...	Bismuth—note overlap.
2–10..	Arsenical in full dose.	41–48....	Arsenical.
10–19	Bismuth—note overlap.	48–59....	Bismuth—note overlap
20–29 .	Arsenical.	60–65 ...	Arsenical
		65–72....	Bismuth—note overlap

If the infant is ill with early congenital syphilis it may do badly under this

the jugular vein is easy of accomplishment: lay the child on the ... head dependent and turned to one side; crying brings out the jugular vein very promptly. Injection may also be made under the fascia of the scalp. Injection into the fontanel is very dangerous. The bismuth is given intramuscularly of course. Astrachan and Cornell (1943) stated that mapharsen can also be given intramuscularly in selected cases in which all attempts at intravenous therapy have failed.

Bismarsen.—This drug has the definite advantages of being given intramuscularly and of containing both arsenic and bismuth. Chambers and Koetter used it in 180 patients ranging in age from birth to fourteen years, the majority being more than three years old; Reilly's series comprised 170 children in about the same age range. The series of 147 cases of Beerman *et al.* (1942) were largely in the later stages equivalent to late latent acquired syphilis. It appears that active lesions heal somewhat more slowly under bismarsen than under the straight arsenicals though the ultimate result is quite as good. All observers are agreed, however, that improvement lags in interstitial keratitis. Stokes and Ingraham (1939) stated the dosage as 7 mg per kilogram (3.5 mg per pound). Injections are given once or twice weekly in courses of twenty with rest intervals of two weeks between courses.

Sulfarsphenamine—This drug may be substituted for mapharsen in the

is, however, one outstanding objection to the drug: it is the most toxic of all

TREATMENT OF NEUROSYPHILIS

It is difficult to avoid the conviction that penicillin, combined in selected

Hopkins Hospital, where the study of penicillin therapy in neurosyphilis was initiated in 1943.

Asymptomatic Neurosyphilis.—The first Johns Hopkins report dealt with the treatment of asymptomatic neurosyphilis, Moore and Mohr (1946) showing that in forty-eight patients with early and forty-three with late asympto-

apy with the use of penicillin Moore and Mohr also felt that the reappearance of an increased cell count or of increased protein, or both, is certainly an indication for retreatment They also believed it wise to retreat patients in whom

of dementia paralytica with penicillin, Reynolds *et al* (1946) reporting on the results in forty-one patients, twenty-four of whom received penicillin alone and the remaining seventeen penicillin concurrently with induced tertian malaria Clinical improvement, and to an even more impressive degree improvement of the spinal fluid abnormalities, followed the therapy, though clinical improvement did not necessarily parallel improvement in the cerebrospinal fluid. However, no case was observed in which amelioration of the paretic manifestations was not accompanied by improvement of the spinal fluid abnormalities In analyzing their results with penicillin alone in the treatment of 101 cases of neurosyphilis, Gammon, Stokes *et al.* (1946) found that some of the best effects on symptoms and signs occurred in the mental breaks, the incoordination, tremors and speech defects of paresis. Six of the eleven paretic patients treated by Koteen *et al.* (1947) with penicillin alone at the New York Hospital obtained remission of the disease th

had been *sustained* approximately two years at the time of the report; four of the five who failed to show significant improvement were badly deteriorated prior to the institution of therapy. However, O'Leary (1947), at the Mayo Clinic, says that he has *never seen a clear-cut clinical remission develop* in a patient with frank dementia paralytica of any type from penicillin alone and that the partial remissions that occur not only are incomplete but are of short duration; but he does find that penicillin plus fever therapy produces complete remissions. Reynolds *et al.* (1946) found the results of the penicillin-malaria combination so superior to those of penicillin alone that they felt the combined therapy to be the treatment of choice, though recognizing that penicillin alone may be necessarily preferred for patients whose age and general physical condition preclude the use of malaria therapy. Both Gammon *et al.* (1945) and O'Leary *et al.* (1946) have been impressed *with the fact that improvement following administration of penicillin comes* within two or three months after treatment while improvement following malaria therapy may not be fully manifested for two or three years thereafter; but Reynolds *et al.* said their findings did not support this position, for in their cases there was evidence of gradual and generally well-sustained improvement especially in the spinal fluid.

Spastic Paraplegia.—In the third study of the Hopkins Group, Tucker (1946) reported his inability to cure or even to arrest the course of Erb's syphilitic spinal spastic paraplegia in four cases

Response of Spinal Fluid Abnormalities to Penicillin Therapy.—In the fourth paper from the Johns Hopkins group, Reynolds *(1947) presented* a study of the spinal fluid abnormalities in the 149 patients with various clinical manifestations of central nervous system syphilis that had been treated with *penicillin,* 111 *receiving* penicillin alone and thirty-eight penicillin concomitantly with malaria therapy. Improvement in the fluids generally was apparent, the cell count and total proteins as a rule promptly becoming and remaining normal; colloidal mastic and Wassermann tests gradually improved and this improvement was well sustained However, the degree and rapidity of improvement could not definitely be correlated with the penicillin dosage, [illegible]

[illegible]

tients treated with penicillin and half-courses of fever at the Boston [illegible]pathic Hospital, the cell count and total protein content of the spinal fluid returned to normal in three to six months and six to nine months, respectively, the strength of the Wassermann titer decreasing more slowly.

Tabes Dorsalis.—In the group of forty-one patients with tabes dorsalis, treated with penicillin alone by Koteen *et al* *(1947), there were in general* no striking improvements in the objective manifestations, but subjective improvement was reported in thirty-three of fifty-seven symptoms com-*plained of by these patients. Gammon,* Stokes *et al.* (1946) found that some of their best results with penicillin were obtained in the relief of lightning pains, and O'Leary (1947) said also that some decrease in the frequency and severity of this distressing symptom had been observed by *him* in about 5 per cent of cases. Reynolds (1947), in summarizing the *Johns Hopkins* experience, said he felt tentatively that the ultimate outlook in tabes dorsalis is for distressingly chronic invalidism and that, since the condition evolves gradually with no immediate threat *to life* or vital body function, it is ad-

visable first to employ the completely safe penicillin alone because these patients are frequently poor fever therapy risks.

Optic Atrophy.—Perhaps the most hopeless group of patients among those exhibiting the late sequelae of acquired neurosyphilis are those with primary optic atrophy, the majority of whom also have tabes. According to Moore *et al.* of the Johns Hopkins group, whose studies published in the period 1938–1942 still constitute the classical literature of the treatment of primary syphilitic optic atrophy, malaria therapy is the most efficacious measure Arseno-bismuth and iodide therapy fail to check the progressive changes in the optic nerve that ultimately lead to complete loss of vision, as testified by Bruetsch (1946) and Wile (1946), but it is possible that penicillin-fever therapy may arrest these cases more often than fever therapy alone

[illegible] essed the feeling that [illegible] ts of a favorable re- [illegible] those obtained with arseno-bismuth; O'Leary (1947) says the responses are "erratic."

Penicillin Dosage.—Stokes *et al* (1946) felt at the time of their report that the dosage should be 4,800,000 units in seven and a half days rather than the lower dosage of 2,400,000 units Rose and Solomon (1947) gave an arbitrary 3,000,000 units combined with a short course of fever therapy, but they felt that the need for retreatment in a little more than one-third of their cases indicated that this is not optimum treatment for late symptomatic neurosyphilis Combined with malaria therapy, the paresis patients of Reynolds *et al.* (1946) received up to 4,280,000 units, but when used alone the dosage ran as high as 10,000,000 units The preliminary recommendations of the Johns Hopkins group for penicillin dosage in individuals with early asymptomatic neurosyphilis with the paretic formula was 6,000,000 to 10,000,000 units in fifteen to twenty-five days (120 to 200 intra-muscular injec-

[illegible] the paretic form of fluid, the com- [illegible] ferred in these late cases also. [illegible] ll group of patients he has found [illegible] as useful as penicillin given round the clock at three-hour intervals in aqueous solution

[illegible]

increased later to 0.2 gm. at four to seven-day intervals if no reaction has occurred. Twelve to twenty injections are a course. But if the patient is ambulatory with only slight signs of cardiac embarrassment at the end of the preparatory bismuth and iodide period, neoarsphenamine is used intravenously; nowadays of course many men are preferring mapharsen. The beginning dose of neoarsphenamine is 0.05 to 0.1 gm., cautiously and gradually increased at weekly intervals to a maximum of 0.3 gm., which may be only rarely exceeded; mapharsen is likewise reduced in dosage and given with equal caution. The course comprises ten to twelve injections. Ideally, bismuth and iodide courses are alternated with arsenical courses without intervals for two years; thereafter, if the general physical condition is satisfactory, long rest periods may be instituted, but it is considered probably wise to give a bismuth course followed by one of bismarsen or one of the above arsenicals once yearly as long as the patient lives. The blood Wassermann reaction is usually "fast" and no attention is paid to it.

[illegible]

or increase in incidence and severity, of anginal symptoms. However, in the experience of Russek *et al.* (1946), who used penicillin in the treatment of fifteen consecutive cases of syphilitic aortitis, including four cases of aortic aneurysm, there was no suggestion of any appreciable danger from this form of therapy. The dosage employed was usually 40,000 units every two hours for eighty-five doses. In one instance only, mild substernal pain occurred intermittently at rest on the third day of treatment, but this disappeared after several hours without interruption of therapy. I should say that as matters stand at present the general practitioner would probably do well to allow the position of penicillin in cardiovascular syphilis to be developed by specialists in cardiovascular research before he uses it in his own practice.

TREATMENT OF LATE (TERTIARY) SYPHILIS

In the diverse cutaneous and buccal manifestations of late syphilis, in [illegible] intestinal and rectal forms [illegible] ction is usually not serious [illegible] x." (See below). Treatment can therefore proceed much as in early syphilis. The older arseno-bismuth type of therapy will usually successfully and rapidly produce healing; indeed, Moore (1945) says that even the largest lesions will cicatrize within forty-two to fifty-six days. However, since most of these patients are in or approaching the years in which cardiovascular or hepatic syphilis, both of which call for a cautious attack, may be expected to occur, *every* diagnostic aid should be utilized to make sure that one of these entities is not present as a complication. Some men favor beginning the treatment always with bismuth and iodides in these cases even though the patient seems to be clear of all syphilitic involvements save those relatively harmless ones which are presenting; progress is thus much slower of course. In late syphilis of the bones and joints, surgical and orthopedic aid may be highly desirable.

Late syphilis of the liver and known gummatous laryngitis call for utmost caution in the therapeutic attack. A Herxheimer reaction at one of these

sites may be fatal; or it has been considered that the patient with hepatic syphilis may die in what Wile called the "therapeutic paradox." This latter is a state of affairs characterized by such rapid healing and cicatrization that the portal circulation is obstructed, with resultant ascites, or the bile ducts are occluded to such extent that the most severe jaundice develops. It is therefore the usual practice in hepatic syphilis to aim at only a very leisurely promotion of reparative processes with bismuth and the iodides. I think it should be noted, however, that in Hahn's (1943) treatment of twenty-five patients with hepatic syphilis at the Johns Hopkins Hospital, he found no evidence that hepatic damage due to syphilis predisposes to hepatic damage due to arsenicals; the "therapeutic paradox" was not observed in any of his cases, though he recommended the initiation of treatment with bismuth and iodides because of the possible presence of lesions in the hilum. Dexter and Tucker (1946) advised that in cases of gummatous laryngitis no sort of treatment should be started until provision has been made for continuous and expert surgical observation.

In benign gummatous lesions in late syphilis, penicillin seems to be as good as but not superior to the older agents on the basis of absolute results alone, but in view of the amount and duration of treatment and the relative non-toxicity of penicillin, it would seem that the antibiotic is the agent of choice. Dexter and Tucker (1946) reported on twenty-one patients with benign late gummatous syphilis treated with penicillin at Johns Hopkins Hospital. Follow-up periods after penicillin treatment in these cases ranged [illegible] from one month to eight years, the mean being 1.6 years. In only one of the cases had therapy at the time of the primary infection been at all adequate as judged by modern standards, this therapy having been of course arsenobismuth. These cases of Dexter and Tucker were entirely an experimental series, hence the total dosages of penicillin ranged widely between 60,000 to 4,000,000 units. However, as a result of their study, the authors said that they favored the use of a minimum total dosage of 2,000,000 units in cases of the type observed by them. In the fifteen patients with a [illegible] (1946) has recorded an extensive destructive gumma involving the center of the face including the nasal septum and hard palate that resisted 2,400,000 units of penicillin but resolved completely under induced malaria therapy. In Dexter and Tucker's patients with osseus lesions symptomatic improvement was rapid but healing and repair occurred slowly. In late visceral syphilis perhaps we had better look upon the position of penicillin, especially as regards its safety in comparison with arsenic, as not yet clearly defined In the Johns Hopkins series clinical visceral involvement was found in two patients in whom there was concomitant cutaneous or osseous involvement, the liver being the organ most obviously affected although the spleen was also enlarged. Relief of pain occurred rapidly in these cases following penicillin therapy but diminution in size of the affected viscera required weeks or months. In three of the twenty-one patients in this series Herxheimer reactions occurred, but they were not of serious moment; all of the patients

increased later to 0.2 gm. at four to seven-day intervals if no reaction has occurred. Twelve to twenty injections are a course. But if the patient is ambulatory with *only slight signs of cardiac* embarrassment at the end of the preparatory bismuth and iodide period, neoarsphenamine is used intravenously; nowadays of course many men are preferring mapharsen. The beginning dose of neoarsphenamine is 0.05 to 0.1 gm., cautiously and gradually increased at weekly intervals to a maximum of 0.3 gm., which may be only rarely exceeded; mapharsen is likewise *reduced in dosage and given with equal caution.* The course comprises ten to twelve injections. Ideally, bismuth and iodide courses are alternated with arsenical courses without intervals for two years; thereafter, if the general physical condition is satisfactory, long rest periods may be instituted, but it is considered probably wise to give a bismuth course followed by one of bismarsen or one of the above arsenicals once yearly as long as the patient lives. The blood Wassermann reaction is usually "fast" and no attention is paid to it.

Penicillin Therapy.—At the time of the present writing not many reports of the use of this agent in cardiovascular syphilis have appeared. Dolkart and Schwemlein (1945) reported two patients with syphilitic aortitis in whom they were forced to discontinue penicillin therapy because of the production, or increase in incidence and severity, of anginal symptoms. However, in the experience of *Russek et al. (1946)*, who used *penicillin in the treatment* of fifteen consecutive cases of syphilitic aortitis, including four cases of aortic aneurysm, there was no suggestion of any appreciable danger from this form of therapy. The dosage employed was usually 40,000 units every two hours for eighty-five doses. In one instance only, mild substernal pain *occurred intermittently at rest on the third day of treatment*, but this disappeared after several hours without interruption of therapy. I should say that as matters stand at present the general practitioner would probably do well to allow the position of penicillin in cardiovascular *syphilis to be* developed by specialists in cardiovascular research before he uses it in his own practice.

TREATMENT OF LATE (TERTIARY) SYPHILIS

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ill[illegible]

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rea[illegible]

were devoid of evidences of cardiovascular syphilis at the time the treatment was instituted and none of them manifested therapeutic shock involving the cardiovascular apparatus during the course of the treatment. Dexter and Tucker say that the use of penicillin is to be preferred in the treatment of patients with late hepatic syphilis. But a Herxheimer reaction would be as undesirable in such a situation if provoked by penicillin as if it had been provoked by arsenic. Stokes *et al.* (1945), in an interim report, recommended that the initial and even the second day dosage of penicillin be halved and the reduction compensated for by prolongation of the course. Olansky (1947) said that at the Gallinger Hospital Rapid Treatment Center whenever the history or physical examination indicates that a Herxheimer reaction would be most undesirable it has been customary to treat the patient with small doses of penicillin for twenty-four to forty-eight hours, the specific dosage being 1000 units every three hours during this period. However, in their recent experience at the Center there occurred six cases of Herxheimer reaction even on these small doses. Olansky therefore considers it advisable to begin the treatment of all late symptomatic syphilis with bismuth before instituting penicillin therapy if accidents are to be avoided.

TREATMENT OF LATENT AND WASSERMANN-FAST SYPHILIS

Here we are concerned with patients recruited from the following classes: (1) those whose early syphilis was ignorantly or willfully not treated at all; (2) those whose early syphilis was inadequately treated; and (3) those in whom lesions of the primary and secondary stages were wholly absent or so slight and transient that opportunities for diagnosis and treatment did not present themselves. But not all individuals who for one reason or another did not obtain satisfactory treatment of their acquired syphilis fall within the present category, for a certain number of them will have earlier presented themselves with one or more of the lesions of late syphilis. The group is therefore whittled down to include only those patients whose sole manifestation of the disease is a positive blood Wassermann or Kahn reaction; such individuals may be said to have "latent" syphilis provided one is sure that the reaction is not falsely positive.

Now what to do when a patient with true latent syphilis is detected? In the first place the thing *not* to do is plunge in, hurly-burly, to "clean him up" with intensive chemotherapy, for to do this may cause irreparable damage. Instead, the patient should be thoroughly examined, with ophthalmologic, roentgenologic and other help as needed from specialists, to bring from below the subclinical level any occult syphilitic lesions that may be present. Once these are found and the cases disposed of through proper classification, which brings with it automatically the correct type of treatment, we must then decide for those still remaining in the latent class whether to treat them or not.

Whom to Treat.—Cases [illegible] into two groups: "early" latency, in which [illegible] ars old and the full defense mechanism has [illegible] "late" latency, in which the patient has had time to develop completely his spontaneous resistance. It seems that practically always in "early" latency treatment should be instituted for the reason that such patients, being usually still quite young and sexually active, are a social menace through their still considerable likelihood to develop infectious relapse; furthermore, the fact that

they are not far removed in years from what was probably wholly inadequate treatment means that the occurrence of precocious tertiarism may still be expected in them But in "late" latency the decision to treat or not to treat has been considered until recently somewhat a matter of expediency. Now, how-

treated, said that (a) the serologic reactions of approximately 25 per cent of untreated or poorly treated persons with latent syphilis become negative spontaneously and remain so over a period of years; (b) in 20 to 25 per cent of untreated or poorly treated patients with latent syphilis some cardiovascular complication will develop when observations are made over a period in excess of thirteen years (the likelihood of developing neurosyphilis seems to be extremely small), (c) there is no relationship between the state of the blood

very clear-cut report of results obtainable and treatment used in late latency, namely that of Kahn and Becker, of the University of Chicago (1942), in which the satisfactory results obtained were better than those obtained by

eight weekly injections of mapharsen and bismuth, three months' rest; sixteen weekly injections of bismuth, six months' rest, ten weekly injections of bismuth; one year's rest, ten weekly injections of bismuth. Becker says that if the patient's blood test is found to be negative at the termination of this treatment he may be placed on observation; if positive he should have a course of bismuth annually, iodides may be given throughout the whole course of treatment It is obvious that the primary features of this treatment scheme are that it begins with bismuth, comprises several periods during which bismuth and mapharsen are being given simultaneously with rest and bismuth periods alone in between, and that it ends with bismuth after succeeding rest periods of increasing length It is noteworthy, however, that

[illegible]

in the prevention of late complications.

Olansky (1947) considers that penicillin even in small doses should not be administered to patients with latent syphilis until a course of bismuth has been given; this opinion is based on the experience, in a busy rapid treatment center, of six cases of late syphilis in which Herxheimer reactions occurred when the patient was receiving only 1000 units of penicillin per day as preliminary dosage.

Wassermann "Fastness."—The mere fact of Wassermann fastness is not in itself of fundamental significance, but the degree of positivity is important for it is the consensus that if a test that has been running through the years with a fairly fixed titer suddenly increases considerably in titer it is an indication that clinical relapse is impending and that the patient should be retreated. The likelihood of such a thing occurring is, however, very small. Of course the [illegible] is not a potential danger to people with whom he [illegible]

and hardly ever thereafter even if no treatment has been given. There is no available evidence that penicillin is any more effective in permanently reversing a persistently positive blood test than the earlier arseno-bismuth therapy. To be sure, Hill (1946) was occasionally able to obtain a negative serologic reaction with penicillin after arseno-bismuth failure, but always upon reexamination it was found that the change had been only temporary. Reynolds (1946), too, strongly makes the point that to subject patients whose serologic tests remain positive following adequate metal chemotherapy to further [illegible] hopes and to waste time and [illegible]

PENICILLIN REACTIONS AND RESISTANCE

The subject of the reactions to penicillin itself is discussed in a special section at the end of the book. At this place it is in order, however, to describe briefly the Herxheimer reaction, which occurs apparently with much greater frequency under penicillin than under arseno-bismuth therapy. Indeed this reaction occurs in the vast majority of cases of early syphilis; Fromer (1947) actually observed it in approximat[illegible] patients. This is of course not really a penicillin react[illegible] of destruction of the spirochetes [illegible] being treated by penicillin, there occurs fever from two to eight hours [illegible] the beginning of treatment, this being soon followed by chills, edema and pain at the site of the lesion, nausea, general malaise, headache and pains in the joints; these symptoms usually persist for twelve to twenty-four hours. The arthralgia and general malaise are more commonly encountered in secondary than in primary syphilis, and in secondary syphilis it is usual for a flare-up of eruptions to occur; eruptions also occur not infrequently in cases of primary syphilis but they sometimes fade again within twelve hours. In early syphilis the Herxheimer reaction is of no moment and does not call for discontinuance of therapy. Occasionally transient and unimportant gastro-intestinal reactions have been noted in syphilitic patients treated

with penicillin. Scott and Clark (1946) reported the case of a patient in whom it seemed that syphilitic nephrosis occurred as a manifestation of a renal Herxheimer reaction following penicillin therapy in early syphilis. That acute syphilitic nephrosis itself may be successfully treated with penicillin has been shown by Barr *et al.* (1946) and Tucker (1946). In a case of late syphilis, Goebel and Grace (1945) reported that after twenty doses of penicillin at three-hour intervals the patient developed fever, decided congestion and some edema of the soft palate, uvula, fauces and pharynx and also indurated, erythematous, edematous, painful areas from four to six inches in diameter on the buttocks at the sites of injection of penicillin; these lesions also occurred on the chest and back and one over the great trochanter of the femur, the latter being at the site of a previous subcutaneous injection of dilaudid. Fluctuation appeared in two of the indurated areas and thick inodorous sterile pus was aspirated from one of them Since non-syphilitic persons were treated without reaction with the same solution of penicillin as was used in this case, Goebel and Grace felt it reasonable to assume that the reaction was due to the action of penicillin on the treponema I have seen no other report of a similar occurrence

Gammon, Stokes *et al.* (1946) reported that during the first twenty-four to thirty-six hours of their treatment of neurosyphilitics some patients showed an exaggeration of neurological signs or symptoms, *i e.*, they developed neuro-Herxheimer reactions Quite frequently in paretic cases a mild increase in mental abnormalities was seen Severe and dangerous reactions occurred in six cases, one patient nearly died in convulsions, one bled into his brain and developed a partial continual epilepsy, and two others had milder seizures One of the latter individuals also became confused and agitated and had hallucinations for the first time. It was said, however, that all of these four patients ultimately became much better but that another paretic became maniacal and ultimately died Increase in tabetic pains also occurred in four cases; in one of these cases this increase occurred in each of two courses of treatment. These observers stated the opinion that if severe reactions occur in neurosyphilitics being treated under penicillin the treatment should be interrupted for a day or two and resumed at low dosage levels; special care they felt was required in spinal syphilis Tucker and Robinson (1946) also reported two Herxheimer-like reactions of a neurologic character that were of alarming proportions. One of the patients developed intermittent convulsions that lasted for fifteen days and the other became completely disoriented and developed an aimless restlessness but not patterned convulsions. Both of

I have seen reports of only two cases in which it seemed that a penicillin-resistant strain of *T. pallidum* was being dealt with One was that of Tyson (1945), whose patient received 2,400,000 units for seropositive primary syphilis without effect However, Crawford (1947) recently pointed out in connection with this case of Tyson's that the failure may have been due to the short period (five days) during which treatment was given, since it is

known that *prolongation of administration* has decided advantages even with relatively lower dosage. The other instance was Reynold's (1946) case of a gumma of the penis that failed to heal with 4,800,000 units given over fifteen days, the lesion healing promptly following therapy with mapharsen and bismuth.

ARSENICAL REACTIONS

In what follows I am considering the reactions only as they occur in the more conservative types of arsenical therapy, for the intensive methods of administration have been abandoned and hence the types of reaction peculiar to them are no longer seen. It should be noted that most of the reactions occur much less frequently with mapharsen than with any of the older arsenicals The analysis of Burton *et al.* (1946) revealed that in the U. S Navy there had occurred 1034 serious reactions, fifty-four of which were fatal, during a twenty-year period in which 1,392,838 injections of neoarsphenamine had been given. During this time 1,006,951 injections of mapharsen had been given with 173 reactions, six of which were fatal. Thus the fatality rate with neoarsphenamine was one to 25,793 and with mapharsen one to 167,825. Of the six deaths due to mapharsen, two were from toxic encephalopathy, and one each was from hepatic damage, acute renal damage, hemorrhagic encephalitis and circulatory collapse. Arsenical dermatitis was the most frequently reported reaction. These Navy data did not reflect the mortality rate from intensive arseno-therapy but only from arseno-therapy of the more extended types.

Precautions To Be Observed with Arseno-Therapy.—Before starting the arsenical course careful physical examination and urine analysis should be made, and the patient's full history should be elicited in order to determine whether one or more of the following conditions obtain. Evidence or history of skin hypersensitivity (chronic urticaria, eczema, seborrheic dermatitis, frequent "rashes") will indicate the necessity of starting with much lower than usual doses. T[illegible] that untreated syphilis adversely affects the course of pul[illegible] of the syphilis checks the progre[illegible] 1938, Goldblatt, 1939). The impression has been that a precautionary lowering of arsenical dosage is advisable and that if the tuberculous state is far advanced and cachectic, bismuth had best at least begin the treatment; yet Smith, who began treatment on this principle in the earlier cases in his series of sixty-nine double infections, increased his dosage up to just about adequate for uncomplicated syphilis toward the end. Riddell and Anderson (1944), and Hoffman and Kalz (1945), found impairment of liver function in a significant proportion of patients receiving arsenical treatment. In hyperthyroidism, Stokes some years ago found such explosive reactivity to the arsenicals that he preferred to control the hyperthyroidism before beginning antisyphilitic therapy. History of marked easy "bruising" should make one very cautious in the use of arsenicals, and evidence on mucous membranes or skin (or reliable history) of purpura is probably sufficient to contraindicate the use of these drugs, tendency to lightly induced and prolonged hemorrhage should also be taken as warning of delicate balance in the blood-forming mechanisms Mild nephritis counsels caution and initial dosage reduction and so does mild diabetes; untreated diabetes, especially if acidotic, had better be controlled before the arsenical treatments begin, unless the patient is in the

advantageous seronegative primary stage of syphilis, which will warrant beginning both treatments simultaneously. Primary anemia necessitates dosage reduction in the beginning, but secondary anemia is usually quickly benefited by the arsenicals; arthritics and hypertensives are often helped. Optic or acoustic nerve involvement necessitates preparatory use of a heavy metal for three to six weeks. Visual disturbances occur with sufficient fre quency under tryparsamide therapy that the drug should be used only witl the greatest care. Patients with preexisting optic involvement, such as contracted fields or abnormal fundi, are more liable to injury than normal patients; but since some of these patients experience a great improvement in their vison under tryparsamide, its routine withholding in these cases is not warranted, though in such cases there should be expert ophthalmologic, and if possible syphilologic, supervision. The most important signs of adverse action of tryparsamide on the optic tract are subjective dimness of vision, flickering or shimmering sensations, or flashes of light; also objective diminution in the visual acuity, contraction of the visual fields and changes in the fundi. The occurrence of subjective symptoms should be thoroughly investigated for an objective basis If no objective signs are found, tryparsamide may be continued with caution. The presence of objective findings, traceable to the drug, is a contraindication to its further use for at least a month, after which it may be very cautiously resumed—but I repeat, this should all be done only with the most expert consultation available. It appears that tryparsamide occasionally activates mental and physical signs and symptoms in a most objectionable way

The meal preceding the injection of an arsenical and the next one following it should consist of nothing more than toast and coffee or tea, and nothing at all should be placed in the stomach for at least two hours before the injection. It is the almost universal custom to place the patient on a high carbohydrate and low fat and protein diet, usually accomplished by forcing the taking of much bread, potatoes and cereals through a great restriction in the allowance of meat, fish, eggs, milk and butter, the belief being that the liver is thus to some extent protected against the hepatotoxic action of the arsenicals Constipation not infrequently disappears during treatment, since the arsenicals tend to induce moderate diarrhea; it is customary in the practice of some men to have a saline cathartic taken on the morning after each injection

Nitritoid Reaction.—This type of reaction (not seen with mapharsen) usually begins shortly after the neoarsphenamine or tryparsamide injection has been started or the bismarsen has been placed in the buttock. There may be sudden intense pain in the back though this is very rare, always, however, there is a quick general or blotchy flushing of the face and neck and injection of the eyes, dyspnea, cough, nausea and anxiety; sometimes, though unusually, the patient vomits at this point, usually the pulse becomes momentarily bounding and then very weak and edema of the face and neck may supervene Sometimes there is loss of consciousness with suspended respiration for a few seconds The symptoms usually persist for half an hour in some degree, sometimes longer. Though frightening to witness, the nitritoid reaction is fatal only in extremely rare instances The often fatal colloidoclastic shock, with somewhat similar symptoms, which occurs as the result of faulty preparation or administration of old arsphenamine, need not worry the practitioner using neoarsphenamine or bismarsen, but he should

be prepared for the patient's thorough fright through one such *nitritoid* experience, and he *must* heed the instructions for *preparation* and *slow administration* if he is to avoid frequent occurrence of this type of reaction with neoarsphenamine.

About the *only effective treatment for the nitritoid* reaction is the immediate subcutaneous or intramuscular injection of 0.5 to 1 cc. of epinephrine hydrochloride (adrenalin) 1:1000 solution—the arsenical injection having been stopped, of course. It is sometimes possible to prevent the recurrence of this reaction by the subcutaneous injection of 1/75 to 1/50 grain (0.8 to 1.2 mg.) of atropine sulfate fifteen minutes before the injection; or epinephrine may be given before the injection instead of after the symptoms have appeared. Ephedrine sulfate is sometimes used, several doses of 3/8 grain (25 mg.) by mouth on the day before and the day of the injection. Whether or not the stuffing of arsenic-sensitive patients with vitamin C has preventive value is not yet determined since the literature is very conflicting, *but Beerman et al. (1943) seem to have produced evidence that the administration* of the arsenical in an ascorbic acid solution possibly has some value. To 114 patients who had previously had bad reactions they gave the arsenicals in an aqueous solvent containing methyl glucamine ascorbate in doses equivalent to 60, 100, or 500 mg. of ascorbic acid and 7 per cent sucrose; about half the patients seem to have been benefited, the solvent containing the 100 mg. dose apparently having been especially useful.

Lacrimation-Salivation Reaction.—A reaction apparently peculiar to mapharsen consists in mild lacrimation with mild to profuse salivation, beginning fifteen minutes to three hours after injection and lasting several hours. The reaction seems to be annoying rather than truly distressing and does not often occur.

Gastro-Intestinal Reactions.—Many individuals are much disturbed by an "etherlike" odor and disgusting taste when the arsenicals are being injected. This may be counteracted by causing the patient to smell bay *rum or* a perfume during the operation (the cheaper perfumes are preferable because of their greater pungency); place on a pledget of cotton and not on the clothing [illegible] ividuals derive

[illegible]

of ethylaminobenzoate on the tongue one-half hour before [illegible] another *one-half* hour after the injection, the purpose being to anesthetize the taste buds on the tongue. Jones (1940) felt that the routine administration of 1/150 grain (0.4 mg.) of atropine sulfate one-half to one hour prior to the *injection, and also the administration of 100 mg.* of ascorbic acid three times daily, were helpful in preventing gastro-intestinal disturbances. [illegible] always [illegible] rdly [illegible] ance [illegible] iate is that it may be a warning of idiosyncrasy for the drug which [illegible] in serious dermatitis or hematopoietic damage *if administration is persisted in*.

Occasionally a patient will have more than the three or four stools which often follow in the few hours after the injection of an arsenical, and it may be necessary to give a dose of castor oil or very rarely an opiate. *Milk toast*, made from boiled milk, for several meals succeeding the injection usually suffices

to check the trouble in patients who have this diarrheal tendency. The drug effect is not lost by reason of these loose stools Severe gastro-intestinal complications are extremely rare. The rubber tubing type of reaction, which has a gastro-intestinal phase, was of serious moment when old arsphenamine was still employed, but this is of course no longer seen.

Many physicians have found their patients experiencing fewer gastro-intestinal reactions under mapharsen than under neoarsphenamine. Levin and Keddie (1942) said that about 90 per cent of patients who have severe gastro-intestinal reactions to the arsphenamines can tolerate mapharsen in therapeutic doses.

Skin Reactions.—Urticaria or a scarlatiniform erythema often occurs during the nitritoid reaction and subsides with it. Or such an eruption, accompanied by fever but not associated with nitritoid phenomena, may be experienced following one of the early injections. These fleeting skin involvements do not usually require any treatment. Generalized itching unaccompanied by dermatitis and following upon the injection of an arsenical is generally looked upon as a warning signal that further arsenical treatment if given at all should be under the supervision of a specialist. Interest in what is known as "ninth-day fever" in Europe was revived in this country some years ago by Keim scarlatiniform or morbilliform eruption occurring on the eighth to twelfth day after one of the early injections, together with chill and fever, pharyngitis, vomiting, pains throughout the body, superficial adenopathy and perhaps photophobia as in measles There may also be subsequent desquamation as in scarlet fever The reaction is nearly always over in five to seven days, but Muir (1937) reported a case which was followed by severe neuritis and later by severe vesicobullous dermatitis and death from toxic degeneration of internal organs In Robinson's (1938) case, which developed after the third injection of neoarsphenamine, treatment was stopped for two weeks, upon its resumption after full recovery of the patient, hepatitis and jaundice developed very promptly. He, as well as Epstein and Levin (1939) and Cañizares and Thomas (1939), reporting six and eleven cases respectively, felt that arsenical treatment should be resumed with caution after one of these reactions, the first dose being reduced in quantity. Leifer (1945) reported fourteen cases in which early continuation of arsenic after the initial reaction led to serious parenchymatous damage in the form of jaundice, agranulocytosis and in some instances nephritis. All of the patients recovered but some only after a prolonged and severe illness. Twelve of the fourteen patients subsequently received intensive penicillin therapy without reaction. There is also occasionally seen a "fixed" type of eruption that does not contraindicate continuance of treatment one or more plaques which redden and swell, perhaps even become bullous, following each injection; residual pigmentation fades very slowly Mendelsohn (1940) reported an interesting case in which sharp pain in the jaw recurred with each fixed eruption.

If to this brief sketch is added the occasional herpes zoster or lichen planus or erythema multiforme type of eruption and the very uncommon eczematous weeping eruption, practically all of the skin involvements will have been covered except the most important one—exfoliative dermatitis, which accounts for many of the deaths occurring with the more conservative types of anti-syphilitic therapy This reaction may occur at any time in any individual. Briefly, the entity has the following characteristics: (a) general flush, with dry or moist dermatitis of flexor surfaces and lower parts of the body, accom-

panied by very severe itching; (b) usually some degree of edema and a septic temperature; (c) *practically* always a sensation of great chilliness; (d) the full picture may be established in a *few hours* after an injection, and death *may occur very early with intercurrent* respiratory or myocardial symptoms; (e) the patient may linger many weeks *or months*, with the skin becoming very scaly and secondarily infected, the body wasting away (*Cannon et al.*, *1942*, redirected attention to the interesting poikiloderma-like changes that occur ultimately *in extremely* rare instances), liver, kidneys, *intestinal* tract and bone marrow becoming involved, and death finally occurring through these *complications* or an intercurrent pneumonia. Any general practitioner having the *misfortune* to have a patient develop exfoliative dermatitis will certainly

Costello and Landy (1945), who observed fifty cases, which is an unusually large series. Sodium thiosulfate was of no value in the thirty patients in whom it was tried. One gram of calcium gluconate was administered intravenously *to ten patients* every other day for six doses, the value of this measure being questionable. Intravenous dextrose was given ten patients in daily amounts of 20 to 50 cc. of a 50 per cent solution or 1000 cc. of a 5 per cent solution, its administration in this manner appeared to be of benefit in detoxifying the patient. Blood transfusions had to be given to three of the patients because of severe secondary anemia. Concentrated vitamin preparations, including ascorbic acid 100 mg. three times a day, were administered but it was impossible to determine their value. Seven patients were given intramuscular injections of crude liver extract, but in several of these cases this therapy had to be abandoned because the patient developed deep abscesses that had to be widely excised and drained; the conclusion therefore was that individuals with exfoliative dermatitis should not be given crude liver extract intramuscularly. It was necessary to administer sedatives to many of the patients because of the nervousness and loss of sleep occasioned by the intolerable itching and burning; the copious drinking of fluids, especially fruit drinks, was encouraged. Costello and Landy's local treatment consisted of the following measures potassium permanganate, starch and colloid baths; body inunctions with boric acid ointment; wet compresses of 1:10 Burow's solution. D'Alibour's solution 1:10 was applied as wet dressings and also used in the bath; wet boric acid
compresses and wet dressings ... of value
in treating areas of secondary ... tment
proved to be a good emollient. ... lieved
the pruritus in the dry stage of the eruption, 40 per cent sulfur ointment proving of little value. A 1 per cent alcoholic solution of brilliant green was efficacious on moist, oozing areas, such as the axillas and inguino-crural regions. Crude coal-tar paste was of value in the patchy dry areas that remained when the universal eruption was undergoing involution. In some instances in which
... extremities
... tional
... tus or

the dermatitis

To discontinue arsenical treatment should certainly be the rule for the general practitioner; whether it may be cautiously resumed in a given case

is a question to be answered only by the experienced specialist in close touch with the patient. Schoch *et al.* (1940) believed, as a result of considerable study, that mapharsen can usually be successfully used in patients after recovery from dermatitis produced by neoarsphenamine but only if the dermatitis has been of lesser severity than severe exfoliative dermatitis necessitating hospitalization; they recommended that mapharsen dosage be begun at 1 mg. and be very gradually built up, *i.e.*, requiring ten to fourteen injections to reach a 40 to 60 mg. dose. However, in Underwood's (1946) patient a polyvalent sensitivity to arsenicals was present fifteen years after a severe exfoliative dermatitis, being manifested by a mild exfoliative dermatitis after one injection of mapharsen and three months later after an injection of tryparsamide.

Hepatic Reaction.—Around the pleasant little point of jaundice and hepatic injury in syphilis there has been spinning a considerable difference of opinion almost continuously since the arsphenamines came into general use. It seems to me that the studies of Wile and Sams (1934), Sager (1936), Hahn (1943), Mitchell (1943), Ottenberg and Spiegel (1943), Beattie and Marshall (1944), Riddell and Anderson (1944), and Hinds and Kalz (1946), most notably among numerous others, have established the following points with reasonable assurance of their truth (a) In a certain exceedingly small proportion of individuals with untreated secondary syphilis, jaundice appears merely as one of the evidences of the generalization of the early toxemia (b) In individuals undergoing treatment with one of the arsenicals, this symptom occurs with much greater frequency, particularly if the drug is neoarsphenamine rather than mapharsen. (c) In most instances the fully developed clinical picture so closely resembles the familiar one of infectious hepatitis (catarrhal jaundice) as to make differentiation of the two conditions impossible save on the basis of history alone. (d) The onset of symptoms may take place at any time during, or as long as ten months after, completion of the arsenical course. (e) In a small proportion of the cases full acute yellow atrophy of the liver occurs: suddenly developing chills and fever, abdominal pain and liver tenderness, vomiting, delirium, prostration, coma, death (f) In neither syphilitic cirrhosis, diffuse hepatitis, nor hepatic gumma—which are generally looked upon as the "typical" forms of anatomic tertiary syphilis of the liver, though Hahn's (1943) analysis of the anatomic findings in sixty-six autopsied cases of late hepatic syphilis revealed almost exclusively findings of a focal gummatous nature—does this picture develop (g) The syndrome is not merely a type of Herxheimer reaction, as might be suspected in instances when it appears following one of the early injections, nor is it the mere recurrence of active syphilis affecting the liver only (hepato-recurrence), as has been contended when it occurs following a lapse in treatment. (h) It does not merely represent the coincidental occurrence of infectious hepatitis in a patient with syphilis, though admittedly the contention of Bigger (1943), and Salaman *et al.* (1944), is arresting to wit, that jaundice in syphilitics under treatment is probably just the familiar infectious hepatitis transmitted from one patient to another by insufficiently sterilized syringes. (i) It is caused fundamentally by the toxic action of the drug on the liver.

Hinds and Kalz (1946) concluded that markedly impaired liver function and significant reduction of prothrombin concentration indicate arsenical toxicity and that therapy should be stopped at once in such cases, though they also remarked that small doses of arsenicals cause fatal reactions in some patients

and that in these instances discontinuing arsenical therapy does not always prevent the development of serious and sometimes fatal sequelae. In their two cases neither vitamin K, vitamin B complex, crude liver extract, nor methionine had any protective value. It is usual practice to push carbohydrates in combating liver damage. Peters *et al.* (1945) divided a series of 150 patients with post-arsphenamine jaundice into three groups which they treated respectively with cysteine, methionine and casein, control patients being observed simultaneously throughout the study. The rate of recovery of the patients was observed clinically and by estimation of the serum-bilirubin levels; a slight but statistically significant increase in the rate of return to normal was noted in the patients receiving cysteine or methionine. Cysteine hydrochloride was given for seven days in two daily doses of 15 grains (1 gm.) in water half an hour before the morning and evening meals; methionine was quite difficult to prepare for administration and would certainly not be suitable for general employment.

Hanger and Gutman (1940) collected a series of twelve cases of jaundice due to intrahepatic obstruction; Freis and Mater (1944) reported such a case following mapharsen administration, and Hartmann and Singer (1946) a case following neoarsphenamine In this type of case the damage is due to blockage of the tiny bile canaliculi rather than to actual injury of the liver parenchyma; Hartmann and Singer concluded that time is the essential requisite for restoration to normal, the lesion running a long self-limited course unaffected by therapeutic measures.

In early syphilitic hepatitis with jaundice in an untreated patient, Stokes advised preparatory treatment with bismuth for three to six weeks before instituting arsenical therapy; certainly most men agree with and follow the practice but the number of such cases is not large and therefore we have no real assurance that arsenicals begun in small dosage would be more harmful than bismuth. Despite the fact that Leonard's (1944) patient, presenting with jaundice, died of acute yellow atrophy after three injections of mapharsen and two of bismuth, she felt that the literature supports the stand that the use of

inconclusive.

Renal Reaction.—It is ordinarily assumed that severe renal damage occurs only as the result of the administration of toxic doses or preparations, but Anderson (1947) reported a case of severe nephrosis, accompanied by purpura and gastro-intestinal disturbances, which followed the administration of a small dose of neoarsphenamine, the patient recovering despite the severity of the reaction. It is possible that in this instance the individual was hypersensitive to organic arsenicals.

Hematopoietic Reactions.—Fortunately, in view of the extremely high fatality rate, arsenic injuries to the blood-forming apparatus are rare. The vast majority of cases are: (a) thrombocytopenic, with typical purpuric or external hemorrhagic features; (b) granulocytopenic, presenting the picture of a fulminating agranulocytosis; and (c) aplastic, with the characteristics manifested when all the cellular elements of the blood have been affected

Young *et al.* (1940) reported a case of fatal acute hemolytic anemia due to neoarsphenamine; the report of this case therefore makes it possible to add another type of post-arsphenamine jaundice to the list of those previously described. Symptoms of hematopoietic injury may appear after any injection in any one of the courses. The consensus has certainly been until recently that no arsenicals should be given to a patient who has manifested in a severe form any of [illegible]
mapharsen causes reacti[illegible]
arsphenamine, there hav[illegible]
was successfully substituted for the older in most instances. For example, the experience of Epstein and Falconer (1940) indicated that mapharsen usually will not cause a reproduction of the purpuric reaction in patients exhibiting this type of dyscrasia; and there are also indications from scattered case reports that mapharsen can often be safely substituted for neoarsphenamine in individuals who have experienced an attack of agranulocytosis from the latter. Nevertheless, one must weigh in the balance also the fact that there are several single case reports of fatal blood dyscrasias following the use of mapharsen. McManus (1946) reported two cases of acute [illegible]

any noticeable effect.

Encephalopathy.—Headache that is severe and persistent and increasing in intensity must be looked upon as a probable prodrome of the greatly feared but fortunately rare toxic encephalopathy. The other symptoms are vertigo, tremor, disorientation, apathy, mental confusion, occasionally nausea and vomiting, convulsive seizures, prolonged chorea, in some instances hyperthermia, and death In the vast majority of recorded cases the encephalopathy has occurred before the fifth injection of the arsenical, the reaction being almost certainly not a Herxheimer but an expression of hypersensitivity to organic arsenicals. BAL (see below) is achieving some fine results in these cases Ransome *et al.* (1945) felt that the survival of their five patients could be attributed to the fact that they placed them in the sitting posture to prevent the onset of cerebral edema, however, the patient of Hipps and Goldberg (1947) went on to death despite this postural treatment. In the pre-BAL period, Stokes *et al.* (1943) described the treatment of encephalopathy as consisting in (a) repeated drainage of spinal fluid, withdrawing 20 to 40 cc daily, (b) dehydration by use of intravenous 50 per cent sucrose solution, 50 to 200 cc., (c) sedation as indicated, (d) epinephrine. Byrne (1947) suggests that double-strength blood plasma is the agent of choice in counteracting cerebral edema. Oxygen inhalations may also be given, but sodium thiosulfate has been shown to be of no value.

Myocardial Injury.—Edge (1946) reported a very interesting fatal case of focal myocardial fibrosis in which the evidence suggested that the lesion was due to neoarsphenamine, the heart lesion having manifested itself on the patient's recovery from arsenical encephalopathy.

Accidental Paravenous Injection.—Treat by withdrawal of needle and immediate injection from another syringe of 20 to 30 cc of physiologic saline solution containing 0.5 per cent procaine hydrochloride (novocaine), placing the solution around and in the infiltrated area. Then complete the arsenical injection at another site. Cold compresses are usually helpful in

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jaundice in which arsenical therapy brought about rapid clearing. [illegible] (1944) compared the results in ten patients who received bismuth during the jaundice with those in eleven patients given no treatment at all and felt that they supported the use of bismuth; but I thought that his findings were quite inconclusive.

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with BAL from one-half to six hours after the development of symptoms the mortality was 20 per cent, while five of the nine patients in whom treatment was delayed for an average of thirty hours died. In general in this group the patients who recovered usually showed definite improvement in from one to

the average time for from 75 to 90 per cent recovery was thirteen days In ten of eleven patients with arsenical agranulocytosis, BAL administration was followed by an increase in the total white blood cell count and an even more pronounced increase in the proportion and total number of polymorphonuclear leukocytes; the eleventh patient died. In three of four patients who had accidentally received massive doses of mapharsen, BAL administration was followed by prompt symptomatic relief without late serious toxic complications; the fourth patient was considered to have received inadequate BAL therapy and he died on the seventh day. I think I should interpolate here that Downing (1947) reported the successful treatment of two individuals who had been given 0.6 gm of mapharsen instead of the intended 60 mg.; BAL administration was begun one hour after the mistake had been made and at the end

disappearance of associated subjective symptoms; thirty-six of these patients had recovered completely in twenty-four to seventy-two hours and all were well in eight days, but since this complication is self-limited it would seem difficult to assess the role of BAL here. In five of fourteen patients with so-called arsenical jaundice, the administration of BAL in relatively small doses was followed by symptomatic improvement, this being associated in three of the five patients with a prompt fall in the blood bilirubin level, however, in seven of the patients there was either no improvement or the improvement was so slow that it could not be causally related to the BAL administration, and in the remaining two patients the effect was debatable. BAL had no therapeutic effects in three patients with aplastic anemia or in two patients with dermatoses following prolonged administration of Fowler's solution.

BAL is administered in oil in 10 per cent solution intramuscularly and usually reaches its maximum effect in two to four hours. Eagle and Magnuson

at four-hour intervals on the first two days, the dosage then being reduced to one or two injections daily for ten days or until complete recovery occurs (b)
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hours for the first two days, the dosage then being reduced to two injections daily for ten days or until complete recovery occurs.

the beginning; later, hot compresses of saturated solution of magnesium sulfate may be used.

Accidental Intra-arterial Injection.—Walsh and Wyatt (1945) reported a severely painful local reaction following an injection of mapharsen, the pain lasting several hours and necessitating the administration of morphine. They believed that an accidental intra-arterial injection had been made because a blood specimen drawn just before the injection was bright red, the pain was immediate and entirely distal to the point of injection, and an anomalous superficial artery was found at the injection site. Except for the severe pain there were no serious sequelae.

Venous Spasm.—When injecting old arsphenamine, with which we are not concerning ourselves in this book, pain along the vein is sometimes observed during or immediately after injection. Such pain has been reported to occur not infrequently if mapharsen is injected *slowly*. An important point noted by Schoch (1936) is that cold, *not* hot applications, laid from elbow to shoulder along the anterior suface of the arm, will quickly stop this pain.

Substitution of Chlorarsen for Mapharsen.—Beerman and Wammock (1947) state that the compound dichlorophenarsine hydrochloride (known both as chlorarsen and dichlormapharsen) can be rated on all counts as an equivalent substitute for oxophenarsine hydrochloride (better known as mapharsen). This opinion was based upon a review of the literature and their own experience in the treatment of 521 patients with early and latent syphilis to whom 8575 injections had been administered. They felt that the somewhat lessened toxicity of this compound should recommend it for employment as a substitute arsenical for patients exhibiting mild reactions to other arsenicals. The standard maximum dosage of chlorarsen is 45 mg. for an adult female and 68 mg for an adult male, to be given intravenously just as is mapharsen. Beerman and Wammock's initial dosage for children is not to exceed 0.5 mg. per kg. body weight, later dosage averaging between 0.5 and 1 mg. per kg. body weight. Astrachan (1946), who employed a drug of this type in 253 patients in early, late, latent, late congenital, and asymptomatic neurosyphilis found it less toxic than mapharsen but also somewhat less potent.

BAL Therapy of Arsenical Reactions.—The substance dimercaprol (BAL) was developed by the British on the theory that if arsenicals injure tissues by attaching to the thiol- groups therein it might be possible to oppose this action, or really to prevent it, by offering in the blood some compound that also presented thiol- groups with which arsenic might combine, then if the resultant compound were relatively harmless one would have an arsenic antidote through having induced the arsenic to spend itself on the introduced substance instead of on the tissues. The success with the new agent was brilliant, first against the vesicant war gas, lewisite (hence British Anti-Lewisite), then against organic and inorganic arsenical compounds, and more recently against mercury and gold compounds also.

The most extensive compilation of cases is that of Eagle *et al.* (1946) who analyzed the results of the treatment of 227 individuals with arsenic poisoning. In the fifty-five patients with arsenical encephalopathy the over-all mortality was 11 per cent; all fifteen patients with relatively mild cases recovered within one to four days, but in the severe cases in which the patient was comatose or convulsing the results varied with the time elapsed since the development of cerebral symptoms. For example, in twenty-four severely ill patients treated

on record (the latest report I have seen is that of Boyette, 1946). Bismuth may induce diuresis and does so probably more markedly than and as often as mercury. Bismuth-induced Herxheimer reactions usually develop more

loss of ambition, asthenia,
"grippe"), gastro-intestinal
disturbances, herpes zoster, agranulocytosis, nitritoid crises, polyneuritis, various exanthemata and dermatoses (exfoliative dermatitis occurs, and erythema of the ninth day was seen twice by Goldman and Clark, 1939), menstrual disturbances. Cohen (1945) reported a case of conjunctival hemorrhage and was able to find a few other reports in the literature of hemorrhage of some sort occurring as a complication of bismuth therapy. Prior to Wolman's (1940) report of two cases of acute yellow atrophy, both in infants, ascribable to bismuth, no clear-cut instances of this serious type of damage had been described However, Kulchar and Reynolds (1942) reported hepatitis as evidenced by jaundice occurring with the use of bismuth at the astonishingly high rate of 1 to 1030 injections, of course such a report, which is in complete variance with most previous experience, cannot be accepted until it can be proved that arsenic is not also responsible in the causation of many of these cases of jaundice or that some of the other factors discussed under hepatic reactions to the arsenicals are not operating.

IODISM

The symptoms are those of a "common cold" plus any one of a number

but in some cases the drug must be omitted or greatly reduced for a time. Fever sometimes accompanies the other symptoms, but fever as the sole manifestation of iodism, as reported in two cases by Katzenstein (1938), must be a rare occurrence Hand (1946) reported the interesting case of a patient in whom temporary complete unilateral loss of vision was associated with a bullous vegetative ioderma in a patient who had not been taking excessive doses of the drug. The possibility of an iodide cachexia, in persons who have been taking the drug regularly for a very long time, must always be borne in mind I think many of these cases pass unrecognized in some clinics

SYPHILIS AND MARRIAGE

Hill (1946) says that his policy in penicillin-treated cases has been to advise postponing marriage until two years after the blood serologic reaction has become negative, provided that during this interval the patient remains free from clinical manifestations and exhibits a persistently negative
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syphilis in the full sense of the definition may safely marry

Modell *et al.* (1946) noticed as symptoms of BAL administration burning or tingling in the nose, eyes, mouth and skin, perspiration and a sense of warmth, pain in the limbs, jaws, abdomen, head, lacrimation, blepharospasm, salivation, vomiting, unrest, apprehension, weakness and fatigue. The heart rate was accelerated and both the systolic and diastolic pressures were usually increased. According to Sulzberger and Baer (1947), the side effects of BAL barely begin at the 2½ to 3 mg. per kg. level when four injections of this size are given at four-hour intervals on two successive days, the incidence of side effects increasing rapidly, however, when the dose is raised to 4 or 5 mg. per kg. It seems that all of the side effects, even when induced on the higher dosage level, have been of a temporary nature, being usually at their maximum at fifteen to twenty minutes after the drug has been injected and lasting in all only about an hour. When BAL is applied to the skin it acts as a whealing agent and cutaneous allergic sensitization to it does occur, but it seems that these effects have not in any case interfered with the use of the drug in com- [illegible]

[illegible]

however, that severe renal disease would contraindicate the use of the agent.

Carleton *et al.* (1946) concluded from their thorough study of the BAL treatment of thirty patients suffering from arsenical dermatitis that in dosage ordinarily employed the agent had no effect on the urinary elimination of arsenic, but Luetscher, Eagle *et al.* (1946), upon the other hand, found that sixteen of twenty-four courses of BAL were followed by a definite increase in arsenic excretion, four by a possible increase and four by no increase; the matter is therefore *sub judice*.

Sulzberger and Baer (1947) say that barbiturates have been recommended as antidotes for the more severe side effects of BAL.

BISMUTH REACTIONS

Though the reactions of a toxic nature that accompany the use of bismuth are many and varied they are rarely severe enough to necessitate an interruption of the treatment for longer than a few days. The commonest of the symptoms is the appearance of a thin violaceous gray line on the gums, indicative of saturation; another symptom of a deleterious nature which is relatively often noted (but not nearly so often as with mercury) is stomatitis; it is usually of a mild sort and disappears promptly upon adjustment of the treatment schedule or dosage. Experience has taught that it is well to examine the urine of patients before beginning the treatments and to use the findings as a quantitative guide to the same. Now and then during the courses the urine even of patients having no preexisting nephritic disturbances will give evidence of a beginning toxic process in [illegible] does not happen so often as with mercury and the con[illegible] with adjustment in dosage or after a [illegible] long-lasting nephritis or nephrosis is rarely observed, though Heyman (1944) was able to report the cases of four patients seen in his hospital over a span of only a few [illegible] of bismuth produced an intensification [illegible] s the effect was tempo- [illegible] veral months, but in the other two death resulted. A few cases of anuria following a single injection are

pression, several degrees of fever with proportional leukocytosis, spinal fluid that is clear but under increased pressure, and great pain from the severe muscular contractions, consciousness is often retained until the end, death usually occurring on the fourth or fifth day. It is said that if a patient survives the eighth day his chances of recovery are very good.

The incubation period of the disease is usually from ten to fourteen days, but in the series of seventy patients reported by Silverthorne (1947) from the Hospital for Sick Children, Toronto, it varied from one day to one month. It is axiomatic that the shorter the incubation period the higher the mortality. Since the prophylactic use of tetanus antitoxin has become more frequent, a local type of the disease with symptoms confined to the neighborhood of the wound is rather often seen. The mistaken tendency is to recognize this as a new entity, though there are records of numerous such cases before the introduction of antitoxin; sometimes these local tetanic foci precede by some time the signs of descending tetanus

Mortality in tetanus is as high as 40, sometimes even 70 to 80 per cent A few recent reports are showing an appreciably lower mortality than this under modern therapy, but it seems unwarranted to eliminate those who die within twenty-four hours of admission, as some authors are doing, in order to obtain the low figures; indeed, Dietrich (1940) felt that probably many of these early deaths are due to faulty therapy since they occur much sooner than they possibly could have done in untreated tetanus. Silverthorne (1947) believes that many patients in recent years have had a less severe type of illness than was formerly seen.

Vener and Bower (1940) reported a second attack of tetanus in the same patient and mentioned five other cases in the literature.

THERAPY

Sedatives.—Graham and Scott (1946) warned that the patient with tetanus can scarcely expectorate through his clenched teeth and can take only shallow breaths owing to the rigidity of the chest muscles, these factors rendering him an easy prey to pulmonary atelectasis; then when sedation is added in sufficient amounts to depress respiration and the cough reflex the susceptibility to pulmonary complications is still further increased Graham and Scott therefore followed the policy, in treating cases seen among wounded German prisoners during War II, of using just sufficient sedative to blunt the edge of

the wound or replacing the stomach tube, temporary increases were made in the basal sedative dose. It was found that 4 to 6 cc. of paraldehyde every three hours by mouth or stomach tube produced about the desired amount of basal sedation in most cases and that 2 to 4 cc. intravenously or intramuscularly accomplished rapid sedation Sodium amytal was also used successfully in this series of cases, 3 grains (0 2 gm.) every three hours by mouth for basal sedation and 5 grains (0.3 gm.) intravenously for emergencies. The patient's tolerance to both of these sedatives usually increased after three or four days and necessitated an increase in dosage or a shift to the alternate drug. Spaeth (1940) used sodium amytal in dosage of 5 mg. per kg. (2.5 mg per pound) body weight, with an upper limit of 240 mg. (4 grains) for children and 480 mg. (8 grains) for adults. Phenobarbital sodium is also satisfactorily employed;

TETANUS

(Lockjaw)

Tetanus is an acute infectious disease caused by the infection of a wound with the spores of *Clostridium tetani.* The wound is usually an accidental one, though the organism has also contaminated burns and bed-sores and suppurative otitis media. Tetanus neonatorum is becoming very rare now that the umbilical cord is properly cared for as a matter of routine, and tetanus following an abdominal operation is also nowadays a rare occurrence. At least three-fourths of the cases are due to injuries on the street, on the farm, in homes, gardens, stables, etc., and only about one-fourth to industrial accidents. That even our modernly constructed, smooth surface streets are still a potential source of danger was shown by the studies of Gilles (1937). Bush (1941) reported an interesting group of five cases (four deaths) attributable to the introduction of a gauze pad into the cervix by an abortionist. The fact is now well established that the organism is harbored to a very considerable extent in the human intestinal tract as well as in that of the lower animals; Bauer and Meyer found spores of definitely toxic strains in 24.6 per cent of 487 specimens of feces from residents of California.

The interesting studies of Lahiri (1939), in India, indicated that there is no such thing as an environmentally acquired immunity to tetanus; *i.e.*, farmers and others exceptionally exposed do not apparently acquire specific antitoxic protection through subclinical infections. The tetanus organism grows best under the completely anaerobic conditions prevailing in deep wounds or those that have become scabbed over, and its growth is also aided by the concomitant presence of pus-producing organisms; the retention of a foreign body in a fresh wound also increases the chances of tetanus developing. However, I think it should be emphasized that in civilian life most of the cases follow upon insignificant wounds because it has become practically routine practice to administer a protective injection of tetanus antitoxin to individuals with large wounds, it is therefore the small wound that is overlooked or forgotten that is dangerous to the civilian.

The tetanus toxin has been isolated and crystallized by Pillemer *et al* (1946). It is the almost universal belief, most recently bolstered by the findings of Roofe (1947), that the toxin produced by the bacillus at the wound site reaches the central nervous system by traveling along the axis-cylinders of nerves or by way of the perineural lymphatics. But this conviction has been disturbed by the studies of Abel and his associates, more recently pursued particularly by Firor, which indicate that the only way the toxin can reach the central nervous system is by the blood vascular pathway; these workers have even suggested that the tetanus toxin in the cord is altered into or liberates a different agent which is transported to and has its lethal effect upon the vital centers. Of such disturbing heresies is our present great epoch compounded.

[illegible] are restless-
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neck and difficulty in chewing and swallowing A [illegible] abdomen makes its appearance very early. The later, more typical, symptoms are frequent convulsions from which the patient does not at any time completely relax, the characteristic lockjaw (trismus), a sardonic facial ex-

above methods of administering magnesium sulfate except the intravenous, the latter being omitted because they thought it too dangerous and because injection by the other routes was very efficacious Dastidar (1943), who used magnesium sulfate in 155 cases in India, preferred the intramuscular route because he felt the intravenous injection was dangerous, the subcutaneous injection painful and the intrathecal injection not practicable.

Antitetanic Serum.—There has been much skepticism in the profession regarding the value of antiserum in treatment, but recent writers seem to be favoring it again. Statistically, it has certainly not been possible to attest its worth for the reason that there are several variable factors: the severity of the case, the length of the antecedent incubation period, the general condition of the patient, (*i e*, his ability to withstand attack of any sort), the amount of prophylactic serum that was used and the coincident employment of other therapeutic measures Likewise, and for similar reasons, the matter of the preferred route of administration of the serum remains a controversial one. Weinstein and Wesselhoeft (1945), stressing the fact that once toxin has become fixed in nervous tissue it cannot be inactivated by antitoxin regardless of how large a quantity is given, say the sole effect of the administration of the antitoxin is the neutralization of the toxic material still circulating in the blood stream and the maintenance of an antitoxin titer high enough to overcome the effect of any additional toxin absorbed from the local focus of infection They advocate the initial intravenous injection of 50,000 units, the intramuscular injection of 50,000 units and the subcutaneous injection of 10,000 to 20,000 units around the wound if one is present, thereafter 10,000 units should be given every twenty-four hours until the condition of the patient warrants cessation of antitoxic therapy. Pratt (1945) found the administration of the antitoxin intrathecally suggestively but not definitely more effective than giving the same amount by the intramuscular or intravenous routes; [illegible]

intrathecal routes of administration are dangerous and that the antitoxin should be given intramuscularly exclusively.

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Many men have employed avertin as a retention enema. Spaeth used 25 mg. per kg. (12.5 mg. per pound) of body weight for the initial average dose to be followed at fifteen- to thirty-minute intervals with about half that dosage according to individual requirements. Sometimes initial dosage may have to be double that stated if the patient is having severe asphyxial spasms. No deleterious effects of avertin, other than slight transient rectal irritation, have been reported, but Spaeth would prefer not to use it if there are renal or hepatic disorders. In one very severe case of tetanus neonatorum in an infant eight days old, Cole and Spooner (1935) used avertin in full adult dosage per pound of body weight and believed that this heroic measure saved the child's life; for twenty-five consecutive days the patient received never less than two instillations daily and for the first thirteen days often as many as four, five, or six. In Pratt's (1945) fifty-six cases studied at the Infants' and Children's Hospital, Boston, the principal sedatives used were avertin and the barbiturates but no definite correlation could be made between the type of sedation and the final result.

Chloral hydrate is very well absorbed from the rectum; 30 to 45 grains (2 to 3 gm.) in olive oil or water every four hours is permissible dosage. Paraldehyde may also be given rectally and was so used in the majority of Yodh's (1937) series of 438 cases in India; 4 drachms (16 cc.) in 2 ounces (60 cc.) of physiologic saline solution by the drop method four-hourly for the adult, varied according to individual requirements. Morphine is valuable but must sometimes be given in doses so large as to be dangerous. As a matter of fact Firor's (1940) investigations indicated that the lethal agent in tetanus (the secondarily formed agent previously referred to) may act chiefly on the respiratory center; if this is proved to be a fact, of course caution in the use of these respiratory depressant drugs would be doubly enjoined, and this would apply also of course to magnesium sulfate (see below).

First used by Blake in a case of human tetanus in 1906, magnesium sulfate has off and on had its advocates but does not seem to have made a sure place for itself. If *complete* relaxation is sought with the drug it may be very dangerous, but used in moderate dosage it should not be. Calcium chloride will very specifically and immediately combat excessive respiratory depression caused by magnesium sulfate; inject 10 to 20 cc. of a 2.5 per cent solution of calcium chloride in physiologic saline intravenously (slowly). The following is a summary of the magnesium sulfate dosage which served Smith and Leighton as a working basis: *Subcutaneous:* 1 to 2 cc. of a 25 per cent solution for each 20 pounds of body weight, four times in twenty-four hours. Should be continued until disappearance of symptoms. *Intramuscular:* lightly anesthetize with ether and deposit intramuscularly 2 cc. of a 25 per cent solution for each 20 pounds of body weight; effect in less than half an hour and lasts two or three hours. *Intravenous:* most prompt but fleeting; effect may disappear in thirty minutes. Dose: 6 per cent solution, at rate of 2 to 3 cc. per minute until relaxation begins. *Intraspinal:* effect in less than half an hour and relief lasts twelve to thirty hours. Anesthetize with ether and inject 1 cc. of a 25 per cent solution for each 20 pounds; second dose, 0.8 cc. for each 20 pounds; only 0.5 cc. per 20 pounds in a child. Arnold and McDaniel (1939) employed all the

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above methods of administering magnesium sulfate except the intravenous, the latter being omitted because they thought it too dangerous and because injection by the other routes was very efficacious. Dastidar (1943), who used magnesium sulfate in 155 cases in India, preferred the intramuscular route because he felt the intravenous injection was dangerous, the subcutaneous injection painful and the intrathecal injection not practicable.

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used therapeutically. When the use of antitoxin is necessary in an individual not protected through previous and present toxoid injections, it nowadays seems probable that the routine employment of 10,000 units intramuscularly would be preferable to the 1500 units so often given. Spaeth (1946) feels very strongly that the 1500 unit package should be discontinued, for in his opinion not until this is done will practitioners get away from the use of this inadequate dose. The larger dose will confer passive immunity for six to ten weeks, and since passive immunity interferes with the development of active immunity it is wise to defer the subsequent immunization of the patient with tetanus toxoid for that period of time. Teare (1944) said that it is the practice in most London teaching hospitals to give prophylactic injections of antitoxin on the

(10,000 unit) dose would make these subsequent injections unnecessary.

Active Immunization With Toxoid.—How many millions of persons—and animals, for tetanus has always taken a high toll among horses—have been injected with toxoid since the method was introduced by Ramon and his associates is not accurately known, but the number is enormous and reactions, which are nearly always mild, are exceedingly rare. Such immunization should be employed by farmers and certain industrial workers and by all others whose occupations or avocations make them especially liable to tetanus infection. The toxoid should also be administered routinely to all children. According to Long and Sartwell (1947), all of our Army military personnel during War II received a series of three subcutaneous injections of 1 cc. of fluid tetanus toxoid at intervals of three weeks, a routine booster injection of 1 cc. one year after completion of the initial series, and an emergency stimulating dose upon the incurrence of wounds, severe burns or other injuries which might result in tetanus. Such a stimulating dose was also administered at the time of the manipulation of old wounds considered to have been potentially contaminated by *C. tetani*. The Navy used alum-precipitated toxoid; the advantage of this preparation is that only two doses are required to induce immunity instead of the three of fluid toxoid. Though I believe it is theoretically considered that alum-precipitated toxoid is antigenically superior to fluid toxoid, it seems that

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procedures been carried out in strict accordance with Army regulations. Boyd's (1946) analysis showed that the incidence of tetanus in the African and European British Campaigns was also negligible though higher than in our own

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in a group of 284 Japanese wounded. Tetanus among civilian unprotected casualties during the Manila operation was also common; Long and Sartwell (1947) say that at least 473 cases with 389 deaths were recorded. It was also reported from Europe that during the Normandy invasion unimmunized German ground forces suffered over eighty cases of tetanus but that there were no cases in the immunized Luftwaffe, fifty-three cases of tetanus also occurred among American-held German prisoners of war in England during the period from September 7 to October 2, 1944.

Long and Sartwell (1947) state that reactions of a sensitization type occurred at the rate of about 63 per 100,000 injections in our Army so long as toxoids containing Witte's or Berna's peptone were used, but that with cessation of the use of toxoids containing these peptones the incidence of such reactions dropped to 2 per 100,000 injections and that indeed before the end of War II the incidence was even lower than the latter figure It therefore seems that tetanus toxoids may be safely injected without routinely performing preliminary sensitization tests However, Peshkin (1945), on the basis of a study of 159 allergic children, concluded that when a child has had basic immunization with two doses of combined alum-precipitated diphtheria and tetanus toxoid and a third or booster injection is given two to four years later, then alum-precipitated tetanus toxoid alone should be used in order to keep local and systemic allergic reactions at the minimum level.

Diphtheria-Tetanus Toxoids Combined.—It is practically routine pediatric practice in the United States to immunize infants and children with the combined toxoids of diphtheria and tetanus which have been amply shown each to exert their antigenic properties uninfluenced by the other. Bigler and Werner [illegible]

tetanus, his principal reason for the routine protection of such children through the use of tetanus toxoid is to make unnecessary the prophylactic administration of antitoxin should they be injured during the summer while on a farm or at a camp McBryde and Poston (1946) showed that a booster dose as low as 0.1 cc. induces a prompt and adequate rise in antitoxic titer in those inoculated as long as five years previously with tetanus toxoid alone or in combination with diphtheria toxoid—it continues to be routine practice, however, to use 1 cc. for this booster dose The two initial injections of the combined toxoids are usually given one month apart.

Combined Diphtheria, Tetanus and Whooping Cough Immunization.— [illegible]

between one and two years of age and were given 0.5 cc., 1 cc. and 1 cc. doses subcutaneously in the deltoid region at about four-week intervals. Blood was drawn for laboratory testing three months after the last injection, and upon the basis of the laboratory findings at least it seemed that the immunity achieved compared favorably with that expected when each of the antigens is given separately. Further study of this method of immunization will be watched [illegible]

[illegible]

question so that, in Mark Twain's phraseology, "a feller could know where he's at."

TONSILLITIS

(See Streptococcal Sore Throat)

TOXOPLASMOSIS

Infection of mammals, particularly rodents, with the intracellular protozoan parasite toxoplasma is world-wide in distribution; a similar organism has also been recovered many times from wild birds but it is not certain that this avian organism is identical with the mammalian toxoplasma. With the appearance of the report of Wolf *et al.* (1939) we became aware that toxoplasma infections occur in man; cases have been found in Europe and in South and Central America as well as in widely scattered areas throughout the United States While it is established that in most instances infantile toxoplasmic infection is acquired *in utero*, the exact method of infection of the fetus is not clear, *i.e.*, perhaps the organisms pass through the intact membranes or through premature ruptures, or they may be acquired through aspiration of infected amniotic fluid or by direct extension from a vaginal infection of the mother. In some instances the mother's blood contains neutralizing antibodies for toxoplasma although she manifests no clinical signs or symptoms of the infection, but there are other cases in which her blood is negative, the infants in these latter cases, however, not showing signs of disease until shortly after birth There is evidence that if a mother gives birth to a child with toxoplasmosis she may in subsequent pregnancies give birth to perfectly normal infants. Sabin and Ruchman's (1942) performance of neutralization tests on a large number of individuals indicated that a mild subclinical infection may exist without producing characteristic signs or symptoms of the disease, Callahan's (1945) findings were confirmatory. Adams *et al* (1946) reported a typical case of toxoplasmosis in a fourteen-year old girl, who recovered and in whose mother and eight of the nine siblings tested there were obtained positive serological tests for toxoplasma though none of these relatives showed any clinical signs or symptoms of the disease. These may have been fully recovered cases, but it begins to appear that such a thing as chronic asymptomatic human toxoplasmosis can exist in Syverton and Slavin's (1946) remarkable case toxoplasma parasites were demonstrated in biopsied gastrocnemius muscle of a sixty-five year old man convalescing from an acute febrile illness of an obscure nature; Tomlinson

(1945) reported the case of a ten-year-old patient in the Canal Zone who died of sickle cell anemia and in whom toxoplasma parasites were found throughout the brain and in aggregates within myocardial fibers at autopsy, these changes not being accompanied by inflammatory changes or necrosis and the patient not having shown symptoms referable to toxoplasma in-

five of their own. In 80 per cent of these infants there was internal hydrocephalus present at birth or appearing shortly thereafter and rapidly progressing. Seventy-one per cent of the patients showed muscular twitchings; muscular spasm, stiff neck and retraction of the head were also common findings Spinal or bulbar involvement was manifest by paralysis of the extremities, difficulty in swallowing or respiratory difficulties. The usual sequence of events was muscular twitching followed by spasticity and generalized convulsions, the other neurologic manifestations frequently not becoming evident until shortly before death. Various ocular signs and symptoms are observed. Jaundice was not an invariable finding but it did occur frequently. Some of the infants showed signs and symptoms of respiratory infections soon after birth, but since intercurrent bacterial infection may complicate the picture it was extremely difficult to evaluate the exciting cause of the lesion In only seven of the eighteen cases was the temperature elevated above normal and in these cases there was nothing characteristic about the temperature curve. In a few of the infants gastro-intestinal symptoms were the first to present, and half of the cases were feeding problems. Cardiovascular disturbances were not often noted clinically but there was a high instance of involvement of cardiac musculature observed at autopsy. Autopsy studies also revealed cerebral calcification in all cases to a degree that could easily have been visualized by roentgenograms, such roentgenograms have been made ante mortem in some reported cases. It seems that the hematologic picture is extremely variable and not of diagnostic significance, though in general the picture is one of leukocytosis with an absolute increase in the number of monocytes and lymphocytes, there being also an anemia that is frequently accompanied by hemorrhagic tendencies. Accordi-

there an elevation of cerebrospinal sugar, there was usually pleocytosis but in general the cell studies were unsatisfactory

Sabin's (1942) report of a fatal instance of toxoplasmic infection in a six-year-old boy was apparently the only instance of death from toxoplasmosis in childhood that has been recorded. But in the report of Cowen *et al.* (1942) there were included six cases in older children who had probably survived an infection in infancy. The common symptoms in these children were healed areas of central chorioretinitis, poor vision, hydrocephalus, convulsions, motor disturbances and some degree of mental deficiency. In nine out of ten cases in older children and adults who showed a similar type of chorioretinitis without other clinical evidences of infection, and in seven children with atypical encephalopathies without retinal lesions, Sabin and Ruchman

(1942) obtained positive serological tests; such tests were also obtained by Crothers (1943) in eight of nine cases in older children. Very little is known about the active form of the disease in adults. Pinkerton and Henderson (1941) reported two cases in which fever, prostration and a maculopapular rash followed upon a brief prodromal period of weakness and malaise, the rash being generalized except for the scalp, palms and soles. In one of the cases there were signs and symptoms of atypical pneumonia and the findings at autopsy in both cases were those of interstitial pneumonia, focal necroses in the spleen and liver, minute focal lesions in the myocardium and also focal lesions in the brain of the one case examined. Toxoplasmata were found in the lesions and in one case they were demonstrated in the blood ante mortem and in the lesions by animal inoculation. Guimarães (1944) reported the case of a youth of eighteen whose disease lasted twenty-seven days and was characterized by high fever, paresis of the lower limbs, nuchal rigidity, dysphasia and monocytosis. Postmortem examination revealed encephalitis, pericarditis, nephritis and a meningo-encephalomyelitis with extensive inflammatory areas. Toxoplasmata were found in the lesions, but the case was complicated by chronic malaria so that the course cannot perhaps be ascribed with certainty to the toxoplasma infection. The adult case reported by Callahan *et al.* (1946) ran a chronic course with definite symptoms referable to the central nervous system and necropsy findings restricted almost entirely to the brain

THERAPY

Sabin and Warren (1942) and Weinman and Berne (1944) found sulfapyridine the most effective of the sulfonamides in experimental animal infections; trial of this drug would certainly seem worthwhile in human cases if diagnosis can be made very early. Augustine *et al* (1944) found penicillin ineffective in experimental infections; neither quinine nor quinacrine (atabrine) has been found of value in such infections, these agents having been tried because of the intracellular location of the organisms

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TRYPANOSOMIASIS

(Sleeping Sickness)

[illegible] leprosy, plague, trypanosomiasis and yellow fever are five [illegible] in this book for the [illegible] entirely within the province of public health authorities or other specialists of great experience.

TUBERCULOSIS

Nowadays we classify systemic infections with *Mycobacterium tuberculosis* into two distinctly different sorts according to whether the body is reacting to the first or the second assault of the organism. The lesion of first-infection tuberculosis is usually microscopic in size and only very occasionally gives rise to signs detectable roentgenologically in the lung or regional lymph nodes. Being also practically always asymptomatic, first-infection tuberculosis is usually not clinically diagnosed, but the positive tuberculin test indicates its

bacilli may remain alive and virulent throughout the remainder of the patient's life, though this occurs in only a very small percentage of the lesions. First-infection tuberculosis is always the same, whether it took place last month or fifty years ago; the infant, youth and adult all react in the same way to the bacillus the first time it attacks, i e, the lesion ordinarily pursues a benign course and regresses while the individual pursues his normal life The theory, propounded some years ago, that a first infection postponed to adulthood is exceedingly hazardous has not been supported by experience, for among the more than 1000 adults who developed primary tuberculosis while under the observation of Myers and his co-workers (1946) in Minneapolis, the first-infection type of the disease was found to be as well tolerated as in childhood and these adults did not subsequently develop significantly chronic reinfection tuberculosis to any greater degree than those who entered the observation group as tuberculin reactors A positive tuberculin reaction merely tells us that a primary implantation of the tubercle bacillus has occurred in the patient, but it does not indicate to us at what time in his life this implantation took place, nor does it tell us whether the individual has the disease tuberculosis Most of us who must sadly confess to being middle-aged or worse are positive tuberculin reactors for the reason that in the years of our infancy and

47.33 per cent, that it had been reduced to 18 9 per cent by 1936, and to 7.7

with it one can rule out large percentages, particularly in the younger age group, who do not need to be x-rayed This statement of Pleyte certainly substantiates the position taken by Myers *et al* (1945) that there is no phase of the examination for tuberculosis which provides as much specific and accurate information for so many people as the tuberculin test.

This is, then, first-infection tuberculosis, a state that in itself is almost

tissues became sensitized to the tuberculoprotein and a state of allergy was established quite comparable to that obtaining in the sufferer from ragweed pollinosis. In the latter, subsequent inhalation of sufficient of the pollen

and symptoms, that is commonly designated "tuberculosis."

The source of the second infection may be exogenous (from bacilli distributed by *some other individual in an infectious stage*), or *endogenous* (the individual's own organisms having escaped into the blood stream, a bronchus, the subarachnoid space, or some other part of the body, through a defect in the walls which were built up around them during the asymptomatic conquering of the first infection). Endogenous reinfection is fortunately rare and usually occurs in infants or young children within three months from the time of the first infection; the most frequent clinical forms are the deadly *tuberculous pneumonia, diffuse tuberculous meningitis, and miliary tuberculosis* Exogenous reinfections are the much more common, chronic and amenable forms: pulmonary tuberculosis, bone and joint tuberculosis, peritoneal tuberculosis, skin tuberculosis, genito-urinary tuberculosis, and so on

Pulmonary tuberculosis, the most common of all the types of reinfection ... occurrence under the age of ten or eleven years, ... that period. Therefore any child having ... *age of ten should be very* carefully observed thereafter for the early signs or symptoms of reinfection. At Lymanhurst Health Center, in Minnesota, Ch'iu *et al.* (1939) made a *ten-year follow-up* study of 1218 children seven years of age at the beginning, 446 positive reactors without clinical lesions and 772 negative reactors. At the end of the study there were nine cases of tuberculosis in the original positive reactors to one in the negative reactors and the mortality ratio between the positive and negative reactors was thirty-eight to one. The annual or semi-annual roentgenogram of ... detect a

... ray

... that will include ... contents and per- ... observation for symptoms, examination for abnormal physical signs, and frequent roentgen examinations to determine whether *the shadow persists* or changes in size Foley and Andosca (1943) felt that the importance of gastric lavage for the detection of tubercle bacilli cannot be overestimated *since 29.2* per cent of their 639 patients with negative sputum were found to be positive by gastric lavage; the statistical findings of Feld (1944), and the observations *of* Myers ... nature. However with regard to the sedimentation ... culous ... er- ... he ... ee-

ment with this

In the code of Hammurabi, written at least as long ago as 2000 B.C., there [illegible]

experiments in 1865. The other outstanding advances of the nineteenth century were Laënnec's remarkable studies with his new stethoscope, Louis' correlation of symptoms and pathology, Trudeau's pioneering in the sanatorium management of patients, and finally, in 1882, Koch's discovery of the causative organism. Throughout the Orient and in some portions of the tropics tuberculosis is still fatally rampant, though parenthetically one should remark that Jews everywhere are relatively insusceptible to the disease, but in the Western world the tuberculosis death rate has been declining very markedly in recent times except for a temporary setback due to the abnormal conditions obtaining during War II. Pronounced and widespread improvements in the economic status of the masses, combined most likely with other factors which we do not understand, have been at work [illegible]

of individuals with open and infective lesions of [illegible]
(d) [illegible]
colla [illegible]

tested that have given a positive reaction has decreased from about 4 per cent when the campaign began in mid-1917 to less than one-quarter of 1 per cent today. The campaign against animal tuberculosis in our country extends to swine also; almost 1,000,000 swine were slaughtered in 1945 because of tuberculous infection. Since the turn of the twentieth century the death rate from tuberculosis in humans in the United States has been reduced about four-fifths, specifically from approximately 200 per 100,000 to about 40 per 100,000, as a matter of fact in large areas of the United States the tuberculosis problem has become a relatively minor one since the death rate is only about 30 per 100,000. According to Myers (1946), the rate is higher after the age of fifty years than at any other time in life, but he points out that when the present elderly persons are replaced by the next generation there should be a decrease in tuberculosis mortality among [illegible]

figures and predictions applied equally to all groups of our population, but unfortunately they do not. Yerushalmy (1946), Chief Statistician of the U. S. Public Health Service, has said that while for whites of all ages, and for non-whites of most age periods, continued progress is being recorded in tuberculosis mortality as compared with total mortality, the fact must nevertheless be recognized that among non-white young adults this is not the case. Particularly among our more than 13,000,000 Negroes there is still a tremendous reservoir of the disease. At present the tuberculosis death rate among colored males is said to be almost two and a half times the rate for white males; among females the corresponding ratio is more than four

to one. Tuberculosis is often an important family disease not because of heredity but because of its spread through the family's contact with open cases. However, Pinner (1945), while avoiding the statement of a definite conclusion in his summary of the studies of a possible hereditary factor that have been performed in various parts of the world, certainly leaves one with the impression that the transmission of an hereditary factor or predisposition is not disproved. It is the clinical consensus that pregnancy has a bad effect upon the course of active tuberculosis though it is extremely difficult to support this view statistically. Of course it is almost impossible for a mother with active tuberculosis to avoid infecting her infant even though, as is almost always the case, the milk itself does not contain tubercle bacilli. Such studies as those of Muschenheim *et al.* (1946), Brean and Kane (1946), and Morris (1946) leave no doubt that tuberculosis is a major occupational hazard for students of medicine and nursing, nurses, physicians and hospital attendants.

THERAPY

In presenting the therapy of tuberculosis I shall be obliged for obvious reasons to omit consideration of the measures applied by specialists in the handling of certain types of the disease, most notably involvement of the bones and joints, the skin and the genito-urinary tract. What follows, therefore, is exclusively a consideration of the treatment of pulmonary tuberculosis save for the recounting of experiences in other forms of the disease in the section on streptomycin.

Preliminary Bed-rest or Immediate Collapse Therapy?—Admittedly nowadays a preliminary period of bed-rest to give nature an opportunity to control the situation before other procedures are instituted is not as often [illegible]

promptly performed, and sometimes lobectomy and pneumonectomy done without much preliminary treatment. I am certainly incapable of estimating the value of this early surgical approach, but I do know it to be the consensus of those experienced in the field that when adhesions prevent satisfactory artificial pneumothorax, or the patient refuses all forms of collapse therapy, postural bed-rest is often helpful. And it seems to me that a very strong case can be made out for postural bed-rest in its own right, for if Dock (1946) is correct in his explanation for the remarkable apical pulmonary localization of lesions in adults, then it follows that at least a preliminary trial of bed-rest is rational in early cases. Dock would explain the apical localization on the basis of the low level of pulmonary arterial pressure and the height of the column of blood from the right ventricle to the apex of the lung when adults are erect. As a result the apex has little or no blood flow and the normal defense mechanism is inhibited during the waking hours. Dock feels that his theory is confirmed by the very low incidence of pulmonary tuberculosis in mitral stenosis with its high pulmonic arterial pressure and the very high incidence in congenital pulmonic arterial stenosis with resultant low pulmonic pressure. Of course the sequel to this theory is that the recumbent posture brings resistance to tuberculosis in the apical regions to the same level as that elsewhere in the lungs. Dock points out that restriction to bed is therefore not enough in the management of

ment and favor immediate collapse therapy. Well, in a dilemma one should seek help from the most unimpeachable source, and so I present the viewpoint of Max Pinner, Chief of the Division of Pulmonary Diseases of the Montefiore Hospital in New York City, Editor of the American Review of Tuberculosis, and author of a classical book on the fundamental aspects of pulmonary tuberculosis in the adult.

Pinner (1945) says that the superior curative effect of collapse therapy to any other known *treatment must be accepted not only on the basis of many* published statistics and on the strength *of every-day* observation but because collapse therapy, following periods of skepticism, over-enthusiasm, pessimism and balanced judgment, continues to be used as a matter of course wherever pulmonary tuberculosis is being *treated today*. He is careful to point out, however, that bed-*rest still* remains the foundation of all therapy of pulmonary tuberculosis whether *or not it be combined* with collapse therapy. Pinner feels that the *clinical* indications for collapse therapy can be *summarized* quite briefly: (a) progressive lesions; (b) cavitations; (c) *failure* to improve (at all or sufficiently) on bed-rest alone. But he would *have this* classification understood to mean that in cases falling in these three categories collapse therapy must be considered but must not necessarily be done. He [illegible] that as long [illegible] held; if on [illegible] tected, collapse therapy should be started in the *absence of definite contraindications; and* when regression ceases, leaving an active lesion again, *collapse* therapy is in order. In short, the principle, according to Pinner, [illegible] sible time when mani- [illegible] He is of the opinion [illegible] with danger and less functionally crippling than healing with collapse, but would have this attitude accepted as an argument not against collapse therapy but against unnecessary and premature collapse therapy. The approximate limitations of spontaneous healing can only be learned through experience. Pinner feels that unquestionably some minimal lesions need collapse therapy and some definitely do not, and he very rationally points out that minimal lesions in their *dynamic potentialities*, and therefore in their therapeutic requirements and prognosis, are no more a homogeneous group than are *tumors of the* [illegible] potential developments, bacteriological findings, systemic reaction, and the multiplicity of factors indicating the constitutional make-up or the vulnerability of the patient. For selected patients in whom the usual collapse measures do not bring about cavity healing, mainly because collapse is prevented by bronchial stenosis, Pinner feels that it will probably eventually be shown that lobectomy or pneumonectomy will be the solution for the problem.

I think that we shall have to rest the case there for the present

Psychotherapy.—Nowadays the psychosomatic fellows are pressing in upon us from all sides. I personally feel that the situation is a somewhat dangerous one since in the best of us there is always the temptation to effect easy simplification by reduction of complex things to a common denominator. There-

fore I have resisted the pressure that has been put upon me to introduce a section on psychosomatic medicine in this book. However, there are certainly many situations in medicine in which it is utter folly to fail to envision a disease syndrome in terms of the patient as a whole, and there are undoubtedly many instances in which no progress whatever toward alleviation of the patient's condition can be made until both patient and physician frankly face the fact that symptoms and signs and even physical findings of a very concrete nature may be, however bizarre it seems, the reflection of some sort of emotional disorientation. There seems to be much evidence accumulating in the experience of many men that personality factors are important in the precipitation and in the maintenance of a state of active pulmonary tuberculosis in some cases Day (1946), for instance, writes that he has often been able to discern very good reasons why tuberculosis or some other similar chronic incapacitation was necessary to some patients at certain junctures and why it would continue to be necessary to them unless something in their life-pattern underwent change To those who embrace this viewpoint disabling illness of any kind provides an escape from reality into another sort of world Possibly a carefully taken psychosomatic history should be included in all cases of active tuberculosis, with selection of suitable cases for psychotherapy—but of course that would be a most difficult thing for most men to do Well then, perhaps a competent psychiatrist should see all of these patients early in consultation. At any rate, I feel that it is becoming increasingly important for us to understand what the psychiatrists are talking about nowadays, however weird the expressions they use or devious their delineations.

Diet and Vitamins.—The opinion of Banyai, expressed in 1934 and reaffirmed in 1947, is corroborated by the experience of all specialists in tuberculosis: (a) the ordinary balanced house diet is adequate for the great majority of patients with pulmonary tuberculosis and, other things being equal, will restore the weight to normal; (b) increase in weight in those below par should be accomplished primarily by proper attention to the disease itself; (c) the use of strange, supplementary, concentrated foods to which the patient is not accustomed is not indicated; (d) overfeeding is both unnecessary and unreasonable and may be harmful in that extra weight taxes

are helpful

A number of independent observations in relatively recent times have indicated that "exhaustion" of vitamin C occurs in tuberculosis and that the

most of their tuberculous patients at or above the normal level. However, these observers found no correlation between the degree or extent of tuberculosis and the plasma ascorbic acid concentrations in their 150 tuberculous patients.

Farber and Miller (1943) concluded from the study of 400 patients that 25 per cent of them had deficiencies in nicotinic acid (niacin) and riboflavin. Getz and Koerner (1943) found the level of vitamin A in the plasma of recently diagnosed tuberculous patients lowered in proportion to the extent of the tuberculous involvement; and Banyai and Cadden (1944) felt that there were

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symptoms usually do not persist in aggravated form long enough to warrant a resort to drugs in their correction. However, when the former is felt to be excessively wasting the patient by its daily high rise it is nearly always possible

the use of atropine sulfate in a dose of 1/200 to 1/100 grain (0 32 to 0.65 mg.)

of 20 to 30 grains (1.3–2 gm.) an hour or two before the sweat is expected repeating the medication once in obstinate cases. Some such formula as the following may be employed.

℞ Camphoric acid .. .. ℨiv 15 0
Compound tincture cardamom to make. . . . ℨvj 180 0
Label Dessertspoonful (8 0 cc) to a tablespoonful (16 0 cc) one hour before sweat is expected

An alcohol rub at bedtime, or a sponge bath with tepid water to which has been added 15 grains (1 gm) of alum per ounce, is also sometimes effective in preventing mild sweats.

may often be accomplished by having the patient inhale a mixture of 10 per cent carbon dioxide and 90 per cent oxygen: (a) spells of strenuous exhausting coughing are prevented and thereby rest is secured for the patient and particularly for the lungs; (b) an unproductive cough is transformed into a useful one, (c) directly after inhalation the amount of expectorated sputum is increased and its character changes from a heavy, thick and tenacious type into a thinner, serous and more watery kind; (d) the use of expectorant drugs and narcotics can be reduced

Hemorrhage.—Keep the patient as quiet as possible with the head propped in such a way that blood will easily flow out of the mouth Mayer (1942) advised against the use of morphine as it favors spread of the disease through retention of infectious clots. Ice-bags on the chest over the suspected site of

theoretical reasons for massive vitamin A administration as adjunctive therapy in pulmonary cases, particularly in the presence of diabetes mellitus.

Cod liver oil has of course been used in the treatment of tuberculosis for more than a century but the only evidence of its value is of the nature of clinical impression rather than of proof. The oil is best given two hours after a meal in a daily dose of 1 to 3 ounces (30–90 cc.). Many individuals who are unable to take the distasteful substance in the beginning may be trained up to it by starting with very small doses. If both the oil and the spoon in which it is taken are kept on ice the odor is much lessened. It is said that the eating of a banana immediately after swallowing the oil is most effective in overcoming the objectionable taste and odor and in preventing loss by vomiting. The U.S.P. emulsion, and the emulsion with malt of the N.F., are satisfactory preparations. The following prescription is an acceptable working model for the writing of an emulsion, the rules being that there shall be at least one-fourth as much acacia as oil to be emulsified and that the flavoring syrup shall not exceed 10 per cent of the total.

℞	Cod liver oil.	℥iv	120 0
	Acacia.	℥j	30 0
	Syrup of thyme	℥vj	24 0
	Water to make	℥vuj	240.0
	Label One or more teaspoonfuls as directed.		

Simple syrup might be substituted for syrup of thyme and flavoring accomplished by addition of 0.4 per cent (of the whole) of the oil of peppermint, spearmint, lemon, orange, or almond. The following formula for an aromatic oil is contained in the Pharmaceutical Recipe Book:

Gluside (saccharin)	0 5
Compound spirit of orange	20 0
Cod liver oil to make	1000 00

[illegible] ne in Califor- [illegible] to study the [illegible]

Care of Digestion.—This is important, for the majority of sufferers from pulmonary tuberculosis have some form of indigestion; care is best accomplished by enjoining slow and thorough mastication and complete rest both before and after meals. Sodium bicarbonate in a dose of 15 grains (1 gm.), or ½ drachm (2 cc.) of the aromatic spirits of ammonia, the former dissolved in warm but not hot water and the latter to be well diluted before taking, will usually dispose of postprandial distress; or, if these fail, the opposite treatment with dilute hydrochloric acid in a dose of 15 minims (1 cc.) may be indicated. It is extremely doubtful whether pepsin or pancreatin is of any value here. Such simple remedies as the drinking of a little hot water before meals or [illegible]

lagging appetite any one of the following excellent U.S P. stomachic mixtures, with a dose of 1 teaspoonful before meals, is of value: compound tincture of cardamom, compound tincture of gentian, compound tincture of cinchona, or the tincture of nux vomica in a dose of 15 minims (1 cc.).

In instances of diarrhea that are not due to extensive intestinal ulceration it is said that the administration of calcium salts by mouth, calcium gluconate

tion with a spray to prevent coughing. Another mixture sometimes successfully employed is known as Lake's pigment, the formula of which is:

Lactic acid	50 0
Solution of formaldehyde	7 0
Phenol	10 0
Water to make	100 0

The phenol in this preparation acts as an anodyne but it is usually necessary to

Galvanocautery, alcohol injection of the superior laryngeal nerve, actual section of the nerve, ionization and tracheotomy are all employed successfully at times by qualified experts

A number of years ago Dundas-Grant called attention to the following practical point: "I wish, however, to indicate a cause of what patients call 'pain,' the relief from which is anxiously desired. In reality it is a painful

night so as to be ready for use when the patient wakes up I am sure that this condition is overlooked while deeper-lying sources of pain are being sought for. It seems a trifling method of treatment, but it gives great relief and is, of course, available to any practitioner if he only keeps the condition in mind and looks for it."

Terminal Opiates.—In the terminal stages of many cases the suffering is very severe Here the opiates in full doses are oftentimes truly a godsend for they enable us to make the last days of these poor unfortunates much less

Geriatrics.

ultimate outcome of this trial. To be sure, some success has already been

recognized and that collapse of a lung drowned in blood is a questionable procedure at best. He said that occasionally one must resort to phrenic nerve crushing or rarely phrenicectomy when all other measures have failed. Amyl nitrite or nitroglycerin is sometimes used to lower blood pressure, but I think this type of therapy illogical in a patient threatened with shock. Hemostatics are of no value.

[illegible]

use of cathartics or enemas to prevent straining at stool is advisable in some instances.

Pleuritic Pain.—The pain accompanying pleuritic inflammation is oftentimes very severe and greatly retards the patient's progress. A few cases will respond favorably to counterirritants: two of the small mustard plaster obtainable at drug stores should be used end to end under the arm, so that one extends toward the nipple region in front and the other over the lower part of the scapula behind. Adhesive-plaster strapping is more often effective, applying the straps to the side with the patient in the sitting position and holding the breath after a forced expiration. In an unfortunately large number of cases, however, it is necessary to resort to opiates, but perhaps demerol will prove to be useful here. Farber (1943) found the injection of procaine a valuable measure; the technic consisted in preliminary barbiturate sedation followed by the injection of approximately 10 cc. of a solution of 1 per cent procaine with 1:25,000 epinephrine hydrochloride into the skin, chest wall and parietal pleura. The relief of pain by the injection of 80 per cent alcohol into the intercostal nerves close to their emergence was also reported a number of years ago.

Laryngeal Pain.—Vocal rest is sheet-anchor therapy, collapse treatment valuable as both preventive and curative agent in laryngeal tuberculosis. For the relief of the excruciating pain which often accompanies deglutition cocaine is used in a spray of 1 to 4 per cent; this is always to be considered dangerous however. Myerson (1946) has reported that of sixty patients with tuberculous ulceration of the larynx treated with sulfanilamide powder spray, those having ulcerations not associated with perichondritis of the arytenoid cartilages were definitely relieved of pain and that they were able to eat, gained weight and became generally improved. Myerson uses a power atomizer with an adjustable tip that can be bent downward so as to direct the powder spray into the larynx; the tongue is held forward by the patient while 5 to 10 grains (0.3 to [illegible] ...lfanilamide powder is blown into the larynx, the treatment being [illegible] an insoluble anesthetic, may be blown [illegible] ferable to employ it in the form of an emulsion, which may be prepared as follows:

Orthoform	12 parts
Menthol	1 part
Almond oil	30 parts
Yolk of egg	25 parts
Water to make	100 parts

This emulsion is too heavy for use in an atomizer, but it can be self-administered through the use of a Yankauer laryngeal medicator. Iodoform is also [illegible] be added to [illegible] nsuffla-

stage in twenty-one, was moderately advanced in nine, and was minimal in two before treatment with streptomycin was begun After treatment for from two to six months with 1 to 3 gm. of the drug a day, definite roentgenographic improvement was observed in twenty-five patients despite the unfavorable trends observed prior to treatment, evidence that pulmonary cavities had closed was observed in twelve patients apparently as a result of treatment;

patients, and in the remaining four patients it had never been demonstrated in the sputum although the diagnosis of tuberculosis was felt to be undoubtedly correct In seven cases the disease was classified as unimproved by this therapy, these patients without exception having far advanced lesions of long *standing, thick-walled cavities and fibrocaseous lesions. Reactivation of the* disease attending discontinuation of treatment with streptomycin was observed in six instances; two of the patients promptly improved when treatment was resumed, one failed to improve upon a second course of treatment, and the remaining three did not receive further treatment with streptomycin Five of the patients in this series died, one of them after the development of a streptomycin-resistant strain of the tubercle bacillus. While upon the subject of

improvement in the general condition occurred and regression was observed in the appearance of pulmonary lesions in the roentgenograms in all four cases

Hinshaw *et al.* treated seven cases of ulcerating tuberculous lesions of the respiratory passages including the larynx, hypopharynx, trachea and large bronchi. In five of the seven cases prompt improvement was observed and recurrences had not been noted at the time of the report although treatment had been completed for a year or more in four of the cases, in the two cases observations were still incomplete.

Seven patients with tuberculous empyema of long standing were treated with streptomycin by the Mayo group. The drug was given both intrapleurally and intramuscularly but in only one of the patients was improvement unmistakably observed.

Fifteen patients in the Mayo Clinic series had cutaneous fistulas from which purulent material containing tubercle bacillus was draining. In each of these patients the cessation of purulent discharge occurred within four to six weeks, but if treatment was suspended at this stage a tendency towards prompt spontaneous reactivation of the process was observed, however, when treatment was continued for several weeks after complete superficial healing had been accomplished an indefinitely long remission of the disease usually occurred In ten of the fifteen patients fistulas healed and had remained closed for periods of four to twelve months at the time of the report.

directly kill it, in the very nature of things it operates at a distinct disadvantage. Another difficulty is that the drug most likely cannot be carried to the [illegible]

sues of the victim of tuberculosis before symptoms are produced, and thus the patient is more logically a candidate for surgical than chemotherapeutic treatment. It has been pointed out by those who are working conservatively with streptomycin that actual healing in tuberculosis must be accomplished by the slow processes of resorption, fibrosis and calcification and that the role of an antibacterial drug is that of blocking the paths for extension of the disease while these healing forces are operating. Finally, a very serious problem in connection with streptomycin's employment in tuberculosis is that presented by the tendency of *Myco. tuberculosis* to develop resistance to the agent and thus relatively quickly terminate its period of effectiveness.

In citing the instances of employment of streptomycin in tuberculosis it should be distinctly understood by the reader that the drug has had only very limited trial as yet, that in none of the small series of cases in which it has been employed have there been adequate controls, and that those who have had most experience with the agent still consider it entirely in the experimental stage.

The largest series of cases of tuberculosis treated with streptomycin is that of Hinshaw *et al.* (1946), of the Mayo Clinic, who reported a summary of observations of 100 cases. There were twelve patients with generalized hematogenous tuberculosis, nine of these presenting clinical evidence of meningitis, two with focal cerebral lesions demonstrated at autopsy, and one with miliary tuberculosis without evidence of involvement of the central nervous system. Six of these twelve patients died, and of those surviving five were still living and at the time of the report had been observed for periods ranging from two to ten months following the clinical diagnosis. One of the patients who had miliary tuberculosis without meningitis showed pronounced improvement both clinically and roentgenographically after two months of treatment. The other four had well developed tuberculous meningitis and it was felt that the lives of these patients had been prolonged for at least several months and the distressing symptoms of the meningitis had been relieved; but it was thought that much more time must elapse before any of these patients could be classified as cured. Unfortunately residual neurological disturbances were present in three of the four patients with arrested tuberculous meningitis. Only one of the patients was clinically well, ambulatory and free of all symptoms, but even this patient was still receiving treatment five months after admission. Hinshaw *et al.* say that they know of at least six other cases of tuberculous meningitis arrested by treatment with streptomycin in addition to the case reported by Cook *et al.* (1946); Krafchik (1946) has since also reported a single case. The treatment of four of the patients of Hinshaw *et al.* consisted of the intrathecal administration by lumbar or cisternal puncture of 100 to 200 mg. of streptomycin every twenty-four to forty-eight hours for two to six weeks. In addition the patients received 2 to 3 gm. of the substance daily by intramuscular injection, this regimen being continued for six months in those who had been under observation for that long a period. None of the patients who died had received intrathecal therapy and none of those who received intrathecal therapy had died at the time of the report.

Hinshaw *et al.* treated thirty-two patients with active progressive pulmonary tuberculosis in which the opinion was held that rapid spontaneous improvement was unlikely to occur; cases in which nonspecific therapeutic measures or collapse therapy might contribute to recovery of the patient, and also cases in which operation was performed, were excluded from the series In the cases in which the agent was used the disease had reached a far advanced stage in twenty-one, was moderately advanced in nine, and was minimal in two before treatment with streptomycin was begun After treatment for from two to six months with 1 to 3 gm. of the drug a day, definite roentgenographic improvement was observed in twenty-five patients despite the unfavorable trends observed prior to treatment, evidence that pulmonary cavities had closed was observed in twelve patients apparently as a result of treatment; thick-walled cavities persisted in six patients despite treatment; and in the rest cavitation was not demonstrable. The organism disappeared from the sputum of thirteen patients, it continued to be found in the sputum of fifteen patients, and in the remaining four patients it had never been demonstrated in the sputum although the diagnosis of tuberculosis was felt to be undoubtedly correct In seven cases the disease was classified as unimproved by this therapy, these patients without exception having far advanced lesions of long standing, thick-walled cavities and fibrocaseous lesions Reactivation of the disease attending discontinuation of treatment with streptomycin was observed in six instances; two of the patients promptly improved when treatment was resumed, one failed to improve upon a second course of treatment, and the remaining three did not receive further treatment with streptomycin. Five of the patients in this series died, one of them after the development of a streptomycin-resistant strain of the tubercle bacillus. While upon the subject of pulmonary tuberculosis one should note that Sanford and O'Brien (1947) have [illegible]

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The experience of the Mayo group in the treatment of fifteen cases of tuberculosis of the genito-urinary tract convinced them that streptomycin possesses some palliative value in the majority of cases of tuberculous cystitis and that it may bring the disease to a state of temporary arrest in a small minority of cases; but in their opinion it is not curative of renal tuberculosis. They found that when the organisms reappear in the urine after prolonged treatment with streptomycin they are likely to show considerable resistance to the effects of the drug.

It was said that in four of the five cases of tuberculosis of bones and joints treated in the Mayo Clinic series apparent response to treatment was noted. In the seven patients in whom streptomycin was combined with radical surgical measures it was believed that the drug contributed substantially to the recovery of the patients through combating postoperative tuberculous complications.

In a group of eleven patients with miscellaneous types of tuberculosis in the Mayo Clinic series improvement was effected under streptomycin in some but not in others; *i.e.*, the drug was apparently used with good results in three cases of tuberculosis of the peritoneum though recent surgical treatment may have contributed to the recovery in one of these cases; it was felt difficult to evaluate the results of treatment in the two cases of primary pulmonary tuberculosis of childhood because of the pronounced tendency to spontaneous healing of primary tuberculosis; good results were obtained in one of three patients with lupus vulgaris.

In an independent series of five patients who had fatal miliary tuberculosis treated with streptomycin and reported from the Mayo Clinic by Baggenstoss *et al.* (1947), evidence of regression and healing of the miliary tubercles in the lungs was observed roentgenologically in four cases, ophthalmoscopically in the choroid layer of the eye in two cases and histologically in the lungs and liver in four cases and in the spleen in three cases The development of widespread tuberculous meningitis apparently was inhibited in one case and was either prevented or cured in two other cases.

Dosage.—The dosage of streptomycin recommended for the treatment of tuberculosis of adults by Hinshaw *et al.* (1946) is 1 to 3 gm per twenty-four hours, this quantity being divided into four or six doses to be administered every four or six hours by deep subcutaneous or intramuscular injection The solution for parenteral administration may contain from 100 to 250 mg of streptomycin per cc. and is preferably dissolved in sterile water. Solutions containing 25 to 100 mg per cc may be employed topically, intrabronchially or in an aerosol spray. In the treatment of tuberculous meningitis intrathecal injections of from 100 to 200 mg. of streptomycin dissolved in 1 to 5 cc. of cerebrospinal fluid or isotonic solution of sodium chloride are given every twenty-four to forty-eight hours by lumbar or cisternal puncture Treatment of ulcerous tuberculous lesions of the hypopharynx, larynx, trachea and bronchi may include both parenteral and aerosol treatment with streptomycin. according to this group of workers, the aerosol being administered by means of the nebulizer in the usual manner, 20 cc. of isotonic sodium chloride solution containing 0.5 gm of streptomycin is used, 2 cc. being nebulized into the mouth each hour for ten hours of the day.

Reactions.—Hinshaw *et al.* (1946) say that the reactions to streptomycin therapy prolonged over such time as is necessary in the treatment of tubercu-

losis are of sufficient severity that treatment frequently must be denied to patients for whom the prognosis of conventional therapy is good. They also said, however, that these reactions are sufficiently mild to be disregarded in cases of progressive tuberculosis that is not amenable to other forms of treatment. The most frequent and uncomfortable reaction observed in their experience is disturbance of equilibrium; but they do not recommend that treatment be discontinued when this occurs for their experience has shown that compensation takes place even though treatment is prolonged. They felt that renal damage is not likely to occur but that until clinical studies on the prolonged use of purified preparations of streptomycin have been completed it should be recommended that renal function be observed closely while the patient is taking the drug. Keefer *et al* (1946), summarizing the employment of streptomycin in 1000 cases of all sorts, reported an over-all incidence of untoward effects of 20.5 per cent. The incidence of reactions increased with the total daily dose: when the average daily dose was over 1 gm there was a striking increase in the number of reactions, patients receiving 3 gm experienced reactions in 46 per cent of instances, and when the daily dose was 4 gm. or more 60 per cent had reactions. The commonest reactions in order of frequency were headache, fever, skin eruptions, flushing of the skin and vertigo, alone or in various combinations. The headache, flushing of the skin and nausea and vomiting are histamine-like effects, and Hinshaw *et al* (1946) found that they do not any longer occur with the purified preparations now available. The skin eruptions and fever may appear at any time from the second to the tenth day of treatment or they may not be observed until after treatment has been stopped, they may last only one day but have been known to persist as long as nine days, and when a patient has had such a reaction he frequently reacts similarly upon readministration of the drug. These are nowadays looked upon as sensitization reactions and it is thought advisable to stop the administration of streptomycin when the skin eruption appears or in any case to reduce the dose and proceed with all possible care and caution. According to Nichols and Herrell (1946), in the average case from 50 to 75 per cent of the streptomycin administered parenterally is excreted in the urine during the first twenty-four hours. Pain, soreness and induration at the site of the local injection of streptomycin occur frequently, but there is reason to believe that this will diminish as more purified preparations become available. Fowler and Seligman (1947) concluded from a study of their material at Halloran General Hospital and cases seen at the Mayo Clinic and the New York Hospital, that a sizable number of cases of deafness, either transient or permanent, will occur with the use of streptomycin of even the best current manufacture if large doses are given over prolonged periods. They stated that as a rule the onset of otic symptoms, should they occur, is on the seventeenth to twentieth day if 3 gm. of the drug are given per day, and Brown and Hinshaw (1946) reported a case in which they started on the eighty-eighth day. Furthermore, in one of the cases of Fowler and Seligman the symptoms started on the first day of the second course of treatment, which indicates of course, but does not prove, that it was the result of sensitization. Presently available evidence indicates that all the neurologic disturbances are caused by the agent itself and hence are ones that we are not likely to see less of as time goes on. A few instances of eosinophilia have been reported, the condition persisting as long as the drug was given.

PROPHYLAXIS

BCG.—The vaccine known as BCG (bacillus of Calmette and Guérin) is made from living bovine tubercle bacilli the virulence of which is reduced by special cultural procedures This vaccine is introduced into tuberculin-negative individuals in whom, according to its advocates, it initiates a benign and self-limiting infectious process which rather rapidly produces a variable degree of resistance against virulent strains of bovine and human tubercle bacilli Most experience with this preparation has been had in France, Scandinavia and South America, but since the introduction of the vaccine by Calmette and Guérin in Paris in 1920 there has not as yet been produced irrefutable evidence of its effectiveness. To be sure, some of the studies indicate a relationship between "vaccination" of this sort and lowered incidence of the disease among *children over a short period of time, but valid statistical proof of long-time* benefits from this procedure are not yet available. Most of the European and South American studies have been made in populations in areas of high tuberculosis mortality where persons were constantly subject to massive exposure to tuberculosis in the practically complete absence of isolation facilities A somewhat comparable study performed in the United States was reported by Aronson and Palmer (1946), who presented statistical evidence of the efficacy [illegible] Indians in whom [illegible]

[illegible] as medical students, nursing students and employees of general hospitals and sanatoriums where exposure is great. The experience of Ferguson (1946) in several general hospitals and tuberculosis sanatoriums in a province of Canada [illegible]

[illegible] New York [illegible]

[illegible] could be made to appear feasible. Since the aim of BCG vaccination is to convert a non-tuberculin reactor into a reactor, it seems to me that the advocates of this procedure rush in to induce in early infancy or in other tuberculin-negative individuals the same state of allergy which it has been the object of our utmost endeavor in this country in recent decades to prevent I am aware of the argument that infection with this attenuated BCG organism may be of a different sort than primary infection with the virulent human bacillus, but it is difficult to put out of one's mind the fact that those who have had the highest incidence of naturally [illegible] early years have the highest death rate [illegible] desirable that further study [illegible] selected groups, but [illegible] measure [illegible] stated [illegible] ession that BC[illegible] of a and lay [illegible]

relatively high degree of protection against tuberculous infection, and Mudd (1947) says that the agent is now given to every newborn child in Soviet Russia and also to populations under special risk such as nurses in tuberculosis hospitals—but these are merely statements of an attitude or policy and prove nothing. It seems to me very significant that in a conference, reported in early 1947, held under the auspices of the Tuberculosis Control Division of the U. S. Public Health Service and attended by many of the leading figures in tuberculosis investigation in the world, it was recommended that studies be carried on in the United States "in order to determine the effectiveness of this vaccine in the control of tuberculosis." It was also recommended at this conference that the vaccine not be furnished to general practitioners for use in individual patients at this time.

Vole Bacillus.—There is considerable experimental evidence that the bacillus isolated by workers at Oxford University in 1937 from field voles is capable of conferring a high degree of protection against tuberculosis in the experimental animal. It is the hope of workers in this field that vole vaccine may in time prove to be of clinical value in man but as yet no significant studies indicating that this is the case have been published to my knowledge.

TULAREMIA

(Rabbit Fever)

Tularemia is an infectious disease of practically all wild rodents through the whole range in size from mice to raccoons, of deer, coyotes, game birds and indeed even snakes; in fact of all the familiar animals of the United States, whether wild or domesticated, it seems that only the horse, cow, pigeon, chicken and turkey have not as yet been convicted with certainty. It is generally believed that rabbits raised under domestic conditions are not naturally infected, probably because of their freedom from ticks, but Guilford (1947) says the record shows that among the 410 cases reported in Wisconsin, infection was ascribed to contact with tame rabbits in seven instances and that this source was probable in an additional three cases. Originally considered to be confined to the United States, where it was first described, it is now recognized that the disease is probably world-wide in its distribution. Human beings usually contract tularemia while dressing the carcasses of infected animals, or through the bite of one of the several flies and ticks that act as vectors, through ingestion of the insufficiently cooked flesh of infected animals, and also probably through the inhalation of the causative organism or its passage into the respiratory tract through implantation in the conjunctival sac. Several instances have been reported in which women have acquired tularemia during pregnancy and later delivered apparently normal infants; I have seen one report, that of Lide (1947), in which the fetus was killed by the disease though the mother recovered. Larson (1945) isolated *Pasteurella tularensis* from the sputum of three persons suffering from tularemia who manifested no frank clinical signs of pulmonary involvement; a few instances have been recorded in which infection has apparently resulted from dressing the wounds of a clinical case or from handling towels used by an infected person. Infection from handling cured pelts is exceedingly rare. The causative organism has been shown to be maintained in standing ponds and disseminated in flowing streams

and it is therefore felt that water-borne infection is possible in both man and animal. *P. tularensis* was discovered by McCoy and Chapin in 1912 but the disease in man has been definitely known to be caused by the same organism only since the work of Francis in 1919.

In the large series of 225 cases reported by Pullen and Stuart (1945), the incubation period usually varied from two to six days; the average was 4 6 days but the extremes were one and fifteen days. The onset of tularemia is sudden, with chills and fever, pains all over the body, vomiting, sometimes diarrhea and often cough, and prostration. Usually after the first few days of fever there [illegible]

per cent of instances. Wells and Tillman (1946) reported a case of rupture of the spleen and Mayants (1946) infection of the bladder. In addition to the systemic symptoms, there is usually pustulation and finally ulceration at the site of infection, and the glands draining the area become swollen and painful; such glandular involvement occurred in 93.3 per cent of Pullen and Stuart's (1945) cases and suppuration of the glands in 22.2 per cent. Sometimes the glands break down only during a recurrent adenopathy several months or years after apparent complete recovery. In 8 per cent of Pullen and Stuart's (1945) cases subcutaneous lymphangitic nodules were observed on the hand, forearm or arm along the route of lymphatic drainage toward the involved axillary nodes. In about the same proportion of instances in this series a usually bilateral and symmetrically distributed eruption occurred most prominently on the arms and neck; it appeared usually during the second or third week and lasted a few days to three weeks or more. In laboratory-contracted cases the local and glandular symptoms are absent, probably because the organism is ingested or inhaled in these instances. Pullen and Stuart (1945) were able to demonstrate agglutinins in the serum during the second week in 213 of 216 cases; in the other three cases they appeared respectively on the fifteenth, eighteenth and twentieth days of illness. One patient, returning to the hospital [illegible] still had a high because [illegible] agglutin [illegible] dermal [illegible] diagnosis may be made with it a week earlier than with the serum [illegible]tion test. Convalescence in tularemia is usually very protracted. Relapses sometimes occur several months to years after apparent recovery, but no true second infection has yet been recorded. Mortality is considered to be about 6 per cent, most deaths occurring at the beginning of the third week in cases that have become of a typhoidal type and in which pneumonic manifestations have been prominent.

THERAPY

Streptomycin.—Since the first report of the employment of streptomycin in the treatment of tularemia by Foshay and Pasternack (1946) the favorable [illegible] investi- [illegible] agent [illegible]mycin, [illegible]

published by Keefer *et al.* (1946), there were included sixty-seven cases of tularemia with sixty-three recoveries The results were striking and immediate in fifty-five and gradual but permanent in eight. According to these observers early diagnosis and treatment by intramuscular injection for five to seven days with an average amount of 1 gm. daily, given in fractional dosage at four-hour intervals, should be the routine procedure in most instances. In the pulmonary and pleural forms of the disease, as well as in the forms with continuous fever without localizing signs, it is considered desirable to give 2 gm. daily for seven days or longer until the disease is under control. In the seven cases of pleuropulmonary tularemia reported by Hunt (1947) the temperature usually declined within twenty-four hours if it was high when treatment was begun, but in many instances it did *not* reach normal values until several days had elapsed, however, in all patients obvious clinical improvement and subsidence of the constitutional symptoms—headache, aching in the extremities, mental lethargy or stupor, and prostration—occurred before the fall of temperature to normal In these cases the results of animal inoculation of sputum or pleural fluid seemed to support the clinical impression that streptomycin treatment resulted in the rapid elimination of *P. tularensis* from the lesions of the lungs and pleura However, in contrast to the marked clinical improvement bserved, there was comparatively slow resolution of the pulmonary consolidaons and pleural effusions, reduction in the size of the regional lymph nodes, d healing of the primary tularemic ulcers. Complete healing of these lesions, hough felt to have been accelerated somewhat by streptomycin treatment, ally required several weeks In a case of Atwell and Smith (1946), in which e was massive pleural effusion, it seemed that the intrapleural administration of streptomycin was very efficacious in eliminating the organism and in ing the formation of fluid, the dosage employed intrapleurally was 0 5 gm. Howe *et al* (1946) treated three patients with streptomycin because of fatigue and intermittent fever persisting months after the acute stage of their illness had passed, there was no obvious response to chemotherapy in any of these patients and one of them displayed sensitivity to the drug At the present time it is still *not* known whether streptomycin therapy will affect the length of persistence of the immune response as revealed by the presence of serum agglutinins.

Antiserum.—It appears that antiserum has reached the end of its rope, which never seemed to me to be a very long one Foshay and Pasternack (1946) say that although they have records of serum-treated cases that compare favorably with any of their results with streptomycin, they could not match the streptomycin results by selecting the same number of case records at random from their serum series They feel that the variability in response to serum therapy is attributable chiefly to differences in individual defense mechanisms and that streptomycin has a distinct advantage in that it acts directly on the bacteria and independently of this defense mechanism. In a recent case of tularemia reported by Kursban and Foshay (1946), the serum was given only until streptomycin could be obtained and in the report it was specifically stated that the combined use of the two agents was not advocated.

Bismuth Therapy.—Jackson (1947) has reported a series of 264 patients, in whom, without awaiting laboratory confirmation, treatment was instituted early on a presumptive diagnosis of tularemia based on the characteristic clinical syndrome and undoubted history of exposure. In this series a specially prepared 2 per cent solution of bismuth sodium tartrate was given intrave-

and it is therefore felt that water-borne infection is possible in both man and animal. *P. tularensis* was discovered by McCoy and Chapin in 1912 but the disease in man has been definitely known to be caused by the same organism only since the work *of Francis in 1919*

In the large series of 225 cases reported by Pullen and Stuart (1945), the incubation period usually varied from two to six days; the average was 4 6 days but the extremes were one and fifteen days. The onset of tularemia is sudden, with chills and fever, pains all over the body, vomiting, sometimes diarrhea and often cough, and prostration. *Usually after the first few days of fever there* [illegible] which persists with marked [illegible]

been involved in fatal cases but evidence of invasion of the meninges has been observed very infrequently. *In Pullen and Stuart's (1945) series of 225 cases* the criteria for diagnosis of tularemic pneumonia were fulfilled in only 9.33 per cent of instances. Wells and Tillman (1946) reported a case of rupture of the spleen and Mayants (1946) infection of the bladder. In addition to the systemic symptoms, there is usually pustulation and finally ulceration at the site of infection, and the glands draining the area become swollen and painful; such glandular involvement occurred in 93.3 per cent of Pullen and Stuart's (1945) cases and suppuration of the glands in 22.2 per cent. Sometimes the glands break down only during a recurrent adenopathy several months or years [illegible] Pullen and Stuart's (1945) [illegible]

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THERAPY

Streptomycin.—Since the first report of the employment of streptomycin in the treatment of tularemia by Foshay and Pasternack (1946) the favorable [illegible] investi[illegible] ent [illegible] cin,

who dramatically renounced a medical career because in one of his early cases a consultant overbore him by diagnosing typhoid fever *without* rose spots The blood pressure is low throughout the attack The tongue is clean and red

invariably seen. Constipation is the rule, when diarrhea occurs it is usually of the "pea-soup" variety Delirium, usually of a canny rather than a violent type, frequently

to the state

lies in a lov

at any time during the course of the disease, the incidence of positive reactors

more than one week, especially if the leukocyte count is normal or low; he

Pullen (1946), however, these authors emphasized the fact that probably the many cases milder than those hospitalized by them would lower the over-all mortality to a figure considerably lower than that which they published. Perhaps 50 per cent of the fatalities are due to toxemia, 15 per cent to perfora-

Case reports of atypical types of typhoid fever have appeared in recent

nously; 1 cc. doses were used for all adult patients and the amount was reduced on an age-weight basis for children (an average child of six years was given one-half to two-thirds the adult dose). The injections were given daily until the temperature became normal and then at two-day intervals until clinical recovery appeared certain. The number of injections given patients varied from four to eighteen. It was said that tularemic pneumonia developed only once in this large series of cases and that no patient died. These results are so striking that one must certainly remain skeptical of them until they are independently confirmed.

Minor Surgery.—Moore *et al.* (1944) reported a case in which there seemed to be striking results from excision of the primary ulcer. Most men experienced in this disease feel that broken down lymph nodes should be undisturbed beyond the use of hot wet dressings, that abscessed nodes should not be incised until they are about to break through the skin, and that excision of such nodes is absolutely contraindicated.

TYPHOID AND PARATYPHOID FEVERS

(*Enteric Fever*)

Typhoid and paratyphoid fevers are acute infectious diseases caused by *Eberthella typhosa* and *Salmonella paratyphi-A*, *S. paratyphi-B* (*S. schottmulleri*) and *S. paratyphi-C* (*S. hirschfeldii*). They are unquestionably separate diseases since an attack of any one of them does not confer immunity against any of the others, nor can one immunize against the paratyphoid organisms by using the typhoid organism only, or vice versa. Nevertheless, these diseases will not be considered as separate clinical entities in this book for the reason that in their symptomatology (save for the relative mildness of the paratyphoids) and their therapeutics they are one and the same. I shall discuss the three under the single designation "typhoid fever."

In typhoid fever the attack is essentially upon the lymphoid tissues of the body, being especially marked by enlargement of the spleen and hyperplasia and ulceration of the Peyer's patches in the intestine. The majority of those who fall ill of this disease are between the ages of fifteen and thirty. There is usually a prodromal period of about one week, during which there is malaise,

one to two weeks, and then falls gradually during a length of time usually twice that required for it to rise; throughout the entire course of the fever there usually occur daily morning remissions of one or more degrees, but it should be remarked that many variations of this typical fever picture are seen. The pulse, too, is characteristic in that in the beginning at least it is much slower than one would be led to expect by the height of the fever; it often contains at some time a dicrotic wave. At about the end of the first week the so-called "rose spots" appear, usually only on the abdomen, in crops of ten or twelve. Though they are present at some time during the course of perhaps 95 per cent of cases it is nevertheless certain that true typhoid does occur without the appearance of these spots; I shall never forget a young practitioner

both delirium and stupor are modified; bed-sores are not often seen in cases that are diagnosed early; anemia is scarcely ever so profound as on the starvation diet; and what is best of all, the patient leaves the bed very little more

has increased it either Relapses seem to occur more frequently, however, under the new treatment.

TABLE 5.—TYPHOID DIET (3000 CALORIES)

Breakfast.	Calories	3 to 4 P M	Calories
Farina (4 tablespoonfuls, cooked)	100	Tea, 150–200 cc.	00
Toast (1 slice, 30 gm. before toasting)	80	Lactose, 50 gm (1⅔ ounces)	200
Cream, 100 cc. (3⅓ ounces) 20 per cent, which is approximately the same as the top 4 inches from a quart bottle of milk *that has stood at least six hrs.*	200	Sugar, 5 gm	20
Butter, 8 gm	62	Cream, 50 cc. (1⅔ ounces)	100
Lactose, 40 gm (1⅓ ounces) To add lactose to milk, boil 15 gm in 30 cc. of water cool and add to milk	160	Crackers, 3 uneeda or 2 soda, toasted	75
Sugar, 20 gm	80	Butter, 8 gm	62
Coffee, 1 large cup	00	Supper	
10 to 10 30 A M		Rice, 25 gm. (1 ounce, boiled)	100
Milk, 200 cc (6⅔ ounces)	140	Milk, 100 cc (3⅓ ounces)	70
Cream, 50 cc. (1⅔ ounces)	100	Toast, 30 gm (1 slice)	80
Dinner.		Butter, 8 gm	62
Eggs, 2	150	Sugar, 5 gm (for cereal)	20
Potato, 1 medium, about	100	Cream, 60 cc. (2 ounces)	120
Bread, 1 slice, or roll, 1.	80	Orange, 1 sliced	100
Butter, 30 gm (1 ounce)	234	Sugar, 5 gm (with orange)	20
Apple, 1 medium sized (pared and cored)	234	8 to 9 P.M.	
Sugar, 15 gm (½ ounce)	60	Cocoa, 5 gm	25
(Potato baked, served with butter. Apple baked with 15 gm sugar, and about 8 gm butter Some patients will eat more butter if the unsalted is used)		Sugar, 10 gm	40
		Milk, 150 cc. (5 ounces)	105
		Cream, 30 cc (1 ounce)	60
		Lactose, 25 gm	100

Proper feeding, then, is the most important element in the treatment of

thousand calories per day is perhaps the optimum amount if we are entirely

(Table 5).

Of course it is not necessary to determine the quantity of calories accurately; the idea is to get as many into the patient as possible. Simple diarrheas will usually respond to an adjustment of the amount of cream (fat) allowed; some-

years: typhoid pyelonephritis without symptoms referable to the intestinal

reported four cases in previously vaccinated laboratory workers who contracted the disease while working with material containing typhoid bacilli and developed an entirely atypical clinical picture and a course less severe than that usually seen in patients who had not been vaccinated. Diddle and Stephens (1939) described a case of probable intrauterine typhoid fever in a baby born of a mother convalescent from the disease.

Typhoid fever is undoubtedly a very old disease, but it was long confused with typhus. The belief was formerly held that certain parts of the tropical

rier." This contact may be direct or indirect: through a contaminated water or milk or ice cream supply, by the ingestion of food over which flies have dragged their infected filth, or the eati
in their feeding or fattening beds, or
dust—this latter method of infection
cases in the British Army during the B

proud. For more than a decade now, the typhoid death rate per hundred thousand in representative large cities in the United States has been below 1.0, whereas in 1910 the rate was slightly above 20.0; even in cities in the South in which the former rate was as high as 35 to 50 it is no longer above 2.0 in any instance.

Typhoid fever, which increases in incidence after June to a peak in late fall and early winter, is by no means the "thing of the past" that it is unfortunately represented to be in some quarters. Fairly recent epidemics have been those at Bournemouth (1936) and Croydon (1937), in England, a severe one in a state hospital for the insane in Illinois (1939), and one in Melbourne (1943). Trailer camps and eating places along much travelled highways have

THERAPY

Dietetics.—It is the almost unanimous clinical impression that full feeding has had much to do with the reduction in the typhoid death rate that has occurred in the last few decades. Certainly the severity of the symptoms is greatly lessened: extreme tympanites is unusual, and when it occurs can often be overcome by a proper adjustment of the diet, diarrhea often yields in the same way and constipation, on the other hand, is less stubborn because there is actually considerable food residue present to be propelled through the bowel;

subsequently spreads over the body, acts as a tonic to the circulatory apparatus; now there are those who cavil at this, but for my own part I still believe that these packs are "stimulant."

Care of the Bowels.—Typhoid fever most certainly cannot be "flushed out of the system," and it would therefore seem, with the ever-present danger of perforation, that we are well advised to leave the peristalsis stimulators out [illegible] uds, or [illegible] accom- [illegible] [2] Many men have relinquished the old favorite, castor oil, but use instead cascara sagrada frequently throughout the course of the disease; however, even this mild emodin cathartic may at times violently stimulate peristalsis. Liquid petrolatum has enjoyed some vogue of late, but I wonder if we will not conclude in time that whatever good may accrue from the employment of this intestinal lubricant is more than counterbalanced by the increased dissemination of the bacilli incident upon the constant leakage of the oil from the rectum

Diarrhea.—On the full feeding regimen diarrhea is seldom a prominent symptom and when it does occur usually yields to a careful readjustment in the cream and lactose portions of the diet, when it persists, resort is usually had to the tannins or to bismuth. Acetyltannic acid (tannigen) may be given in a dose of 8 to 10 grains (0 2–0.6 gm), four times per day, taken dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids Protan is given in 5-grain (0 3 gm) tablets; from 2 to 6 of which may be given at intervals of two hours or more. Albumin tannate (albutannin or tannalbin) must be given in doses of 30 grains (2 gm.) or more, in capsules or as a powder. For the employment of bismuth the following is a satisfactory prescription

℞	Bismuth subcarbonate	ʒj	30 0
	Glycerin	℥ss	15 0
	Syrup of ginger to make	℥iv	120 0
	Label, 1 teaspoonful every two hours for 10 doses.		

It is well to avoid the use of opiates in typhoid if possible for the reason that meteorism is likely to follow their withdrawal

Tympanites.—When this symptom does not yield to dietary adjustment it should be treated as described in the discussion of pneumonia, though of course *resort must never be had to pituitrin as there mentioned*

Delirium.—Dissuasion is the best sedative in the treatment of typhoid delir[illegible]

dr[illegible]

In [illegible]

to be used carelessly however·

℞	Sodium bromide	ʒvij	28 0
	Chloral hydrate	ʒvij	28 0
	Peppermint water to make	℥iv	120 0
	Label 1 teaspoonful in water every three or four hours.		

times the lactose has also to be reduced. It is well to bear in mind that if a patient has aversion for particular foods when well he will continue to dislike them when ill. Schoffman (1941) thought that the use of large amounts of ripe banana was provocative of good results in a small number of cases in children. Some patients cannot tolerate milk in any form or amount; Table 6 comprises a diet without milk that was, and possibly still is, in use at the University of Michigan Hospital.

TABLE 6.—TYPHOID DIET WITHOUT MILK

6.30 A.M.	Cup of hot coffee, sugar, 2 drachms (8 gm.); 2 slices of zwieback or toast, butter
8.30 A.M.	One portion of oatmeal or Robinson's prepared barley, with 6 buttered crackers, saltines.
10.30 A.M.	[illegible]
12.30 P.M.	[illegible]
2.30 P.M.	[illegible]
4.30 P.M.	2 ounces (60 gm.) of rice, farina or cream of wheat mixed with 1 ounce (30 gm.) of butter and 4 drachms (16 gm.) of sugar.
6.30 P.M.	3 slices buttered toast.
8.30 P.M.	6 ounces (180 cc.) of soup.

Fluids, Chlorides and Vitamins.—Since the patient has fever and is losing a considerable amount of water and salt in consequence, fluids should be given liberally and salt added in considerable quantity to the food or given in the form of the commercial tablets. Most patients will take lemon- or orangeade when they rebel at plain water. When the patient's interest cannot be sufficiently aroused to ensure the taking of fluids by mouth, resort should be had to hypodermoclysis or proctoclysis with physiologic saline solution. If an adequate diet is not being taken, of course it will become necessary if this state persists very long to begin administration of vitamins in concentrated form; in fact, Stuart and Pullen (1946) feel that vitamin therapy is indicated in all cases.

Care of Mouth and Skin.—The tongue and mouth tend to become very foul, and the lips cracked and sore, in typhoid fever. The teeth should be kept well brushed and the mouth washed at sufficient intervals with the N.F. alkaline aromatic solution; it is well to anoint the lips with glycerin and water. A daily cleansing bath with soap and water should be given, to be followed by an alcohol rub; areas especially liable to the development of bed sores should have alcohol applied to them several times daily and be kept well powdered in the interim. These things have a double purpose: first, they make for the greater comfort of the patient and serve the ends of ordinary cleanliness, and second, they serve to keep up the morale of the patient; to this latter end he should be encouraged to participate actively in the daily routine procedures as much as is possible consistently with the avoidance of fatigue.

Control of Temperature.—The new tendency in the therapy of all acute fevers is to look upon the rise in temperature as a physiologic process and to direct no drug treatment toward its reduction, and undoubtedly many lives have been thus saved; but I cannot hold with the extremists who would totally disregard all antipyretic measures. External hydrotherapy seems to me a [illegible] bath, nor perhaps [illegible] vater and alcohol, [illegible] 03° F. (39.4° C.), and a carefully applied cold pack (the patient to be placed on two blankets

subsequently spreads over the body, acts as a tonic to the circulatory apparatus; now there are those who cavil at this, but for my own part I still believe that these packs are "stimulant."

Care of the Bowels.—Typhoid fever most certainly cannot be "flushed out of the system," and it would therefore seem, with the ever-present danger of perforation, that we are well advised to leave the peristalsis stimulators out of the picture altogether. On the full diet treatment, a small soapsuds, or better still physiologic saline, enema at a regular time each morning accomplishes the daily evacuation of the rectum, and what more is needed? Many men have relinquished the old favorite, castor oil, but use instead cascara sagrada frequently throughout the course of the disease; however, even this mild emodin cathartic may at times violently stimulate peristalsis. Liquid petrolatum has enjoyed some vogue of late, but I wonder if we will not conclude in time that whatever good may accrue from the employment of this intestinal lubricant is more than counterbalanced by the increased dissemination of the bacilli incident upon the constant leakage of the oil from the rectum

Diarrhea.—On the full feeding regimen diarrhea is seldom a prominent

in a dose of 8 to 10 grains (0 2–0.6 gm), four times per day, taken dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids Protan is given in 5-grain (0.3 gm.) tablets; from 2 to 6 of which may be given at intervals of two hours or more Albumin tannate (albutannin or tannalbin) must be given in doses of 30 grains (2 gm.) or more, in capsules or as a powder For the employment of bismuth the following is a satisfactory prescription·

℞	Bismuth subcarbonate	℥j	30 0
	Glycerin	℥ss	15 0
	Syrup of ginger to make	℥iv	120 0
	Label 1 teaspoonful every two hours for 10 doses		

It is well to avoid the use of opiates in typhoid if possible for the reason that meteorism is likely to follow their withdrawal.

Tympanites.—When this symptom does not yield to dietary adjustment it should be treated as described in the discussion of pneumonia, though of course resort must never be had to pituitrin as there mentioned.

to be used carelessly however.

℞	Sodium bromide	ʒvij	28 0
	Chloral hydrate	ʒvij	28 0
	Peppermint water to make	℥iv	120 0
	Label 1 teaspoonful in water every three or four hours.		

In rare cases nowadays is it necessary
its more frequer
of severe cases

Circulation.—

form of typhoid fever are no longer seen in these days of adequate feeding When there is occasional need for a drug, however, metrazol is probably the drug of choice One should perhaps note, too, that many men still prefer ½ to 1 ounce (15–30 cc.) of whiskey, three or more times daily, for "stimulation" in typhoid fever.

Hemorrhage.—Keep the patient absolutely quiet by the use of morphine sulfate, ⅛ to ¼ grain (8 to 15 mg.), or dilaudid, 1/32 grain (2 mg.), every three or four hours; this will also splint the bowel. Withhold all food, and nearly all water, until the bleeding has apparently stopped. Apply continuous cold to the abdomen. Hemostatics are of no value.

Perforation.—Surgical intervention as soon as the diagnosis is made—which is easy to write but difficult of accomplishment for the reason that the diagnosis is oftentimes extremely hard to arrive at and very often a surgeon *with the skill here needed* is not at hand.

Specific Chemotherapy.—As ordinarily employed, neither the sulfonamides,

indicate to be expected at least in the case of penicillin. In Palestine, Reitler and Marberg (1943) employed tin in a small series of cases with results that seemed to indicate some value for this agent. More recently Reitler (1947) has kindly informed me that he has performed another study, better controlled than the original one, with findings again indicative of some action of the metal upon the organisms in the intestinal lymphatics but not in the blood stream or in the bile ducts. It seems unfortunate that a large-scale study of this agent in typhoid cannot be got under way.

Bacteriophage.—Treatment by means of type specific bacteriophage seemed a very promising and safe procedure in the hands of Knouf *et al.* (1946) at the Los Angeles County General Hospital The patient's organisms were obtained from a culture of his own blood and then high potency bacteriophage specific for his type of *E. typhosa* organisms was prepared, which incidentally was said not to be invariably possible because some strains of the organism do not type. An injection of 1 cc. of this bacteriophage material in 500 cc. of dextrose solution was then allowed to drip intravenously over a period of four to seven hours. A chill and fever reaction is experienced during the 'phage administration but the temperature had returned to normal within nine and a half to twenty-four hours in all of their cases The series comprised fifty-six patients and it was said that a striking thing with regard to the treatment was the marked change in the course of the infections regardless of the stage of the disease in which the patients were treated; the mortality was a little more than 5 per cent. In about 10 per cent of the patients there occurred a clinical and bacteriologic relapse that was said to have been amenable to repeated treatment; cultures of blood from all the other patients became immediately and permanently negative. It would seem, therefore, that in the majority of instances the patients were cured by crisis since the blood cultures were negative twenty-four hours after treatment and continued so, there was ab-

sence of fever after treatment, and immediate clinical improvement occurred. The rapidity with which the patient returned to his normal mental outlook was declared the most spectacular objective accomplishment of this bacterio-

the results of such trial will be awaited with interest.

Specific Serum.—As the result of the work of Felix and his associates, a so-called "Vi + O" antityphoid serum has been made available; it is considered that in this serum two antibodies have been effectively combined, the "Vi" element conferring protection by suppressing the multiplication of virulent strains of *E. typhosa* and the "O" antibody neutralizing the endotoxin of that organism Clinical trials of this new antityphoid serum have been reported from Palestine, Ireland, England, South Africa, China, India and Malaya. The most recent report I have seen, that of Hodgson (1944), who used the serum in twenty-five cases in Liverpool, indicated that the agent is

PROPHYLAXIS

Care of the Patient.—Everything and everybody coming in contact with

lute cleanliness in the room or ward, by screening out and exterminating flies, by insisting that the attendants frequently change their clothing and wash

death from intercurrent disease, the population is tending to sterilize itself by a combination of the several processes. So the carrier problem, though now probably one of greater importance in specific instances than ever before because of the fact that these reservoirs of infection remain the only sources of contamination in many areas, is upon the whole a problem of declining magnitude. The highly interesting studies of Anderson (1936) and his associates of the Massachusetts Department of Health suggested that contrary to previous belief the more recently a carrier has become such the greater menace he is in general; *i.e.*, the carrier of many years' standing has so infected or immunized the immediate environment that new cases will not develop until fresh susceptible material is introduced, or until such a carrier in later life is obliged to go roaming and is placed in dangerous juxtaposition, as through a food-handling position, to a fresh population.

It seems to be currently the opinion that cholecystectomy for the removal of "nests" of bacilli in the gallbladder is of established value, though only a few years ago the measure was looked upon with considerable disfavor. Saphir *et al.* (1942) felt that treatment with soluble iodophthalein should always be

patients being kept on a low-fat diet to avoid if possible unnecessary contractions of the gallbaldder. The dye was given in the early morning as it was felt that in this way the maximum dye concentration in the gallbladder would be reached at night when repose and the absence of food intake would permit gallbladder rest.

always a local reaction of some severity; if, for any reason, the

been chosen for the injections, a more painful reaction must be expected even

the thigh is so severe

which

lls and

fever, backache, headache, muscular pains, and in some cases nausea and vomiting and even diarrhea. Most individuals experience some degree of this reaction after one or more (usually the middle) injections, but it usually lasts not more than twenty-four hours and can be minimized if the patient remains inactive after the injection.

After the fifth month of pregnancy women are usually not vaccinated, nor are menstruating women, nor infants under two years. Lopez-Rizal, Arguelles and Lara, in Manila, showed that nursing infants are immunized by vaccinating the mother. Nephritis, endocarditis and fever from any cause whatsoever are looked upon as contraindications to vaccination. Expert opinion now seems to hold that it is prudent to refrain from vaccination in all cases of active

tuberculosis and in all "arrested" cases unless the danger of typhoid itself is very great.

The adult dose is 0.5 cc. for the first injection and 1 cc. for each of the two subsequent injections. I find three "rules" for dosage in children above two years: (a) Adjust the dose accordingly as the weight varies from that of the average adult, taken to be 150 pounds (b) One twentieth of adult dose between two and four, and ½ between four and twelve years (British Med. Assoc. Spe-

Maximum protection is certainly had within two or at most three months

study of Ramsey, in 1935—showed that certainly after completion of the three injections, *i.e.*, after two weeks, but doubtfully after only one or two injections, *i e.*, after only one week, the case incidence was significantly reduced Schütze's (1930) animal experimentation certainly yielded evidence in support of vaccination during an epidemic.

It is not yet definitely known how long immunity lasts after typhoid vaccination. Longfellow and Luippold's (1940) mouse protection tests indicated that revaccination of the human with a single dose of 0.1 cc. of vaccine intracutaneously (relative freedom from reactions), or 0.5 cc subcutaneously, reliably renews immunity and that such revaccination should preferably take place each year and certainly at not longer than two-year intervals According to Long (1944), it is the practice in the United States Army to maintain immunity by the subcutaneous administration of 0.5 cc. of the vaccine each year; a similar dose is administered in the event of actual or potential exposure to typhoid or paratyphoid fever.

VINCENT'S ANGINA

(*Fusospirillosis, Trench Mouth*)

This is an acute infectious disease that seems to have been endemic throughout the world for a long time but was not forcibly brought to the attention of more than a few physicians and dentists until it became epidemic in the armies

lesions are single or multiple small red areas that become gray sloughing patches and finally ulcerate and are covered with a yellowish-gray pseudo-membrane; the latter is easily removed and displays a bleeding surface beneath, but it soon becomes covered over again. The breath has nearly always a fetid odor and the interference with eating may be great due to the pain of chewing and swallowing; there is often an adenitis, but only in exceptional cases are there

acriflavine (trypaflavine), hexylresorcinol solution, and potassium chlor
saturated solution. The careful studies of Reasoner and Gill, as long a
1927, showed that solutions of ordinary toilet soaps, as well as pure
prepared in the laboratory, have a definite spirocheticidal effect and that
use in dentifrices assists in keeping the oral cavity free from mouth spiroc
and thus presumably affords a measure of protection against tissue infe
with the Vincent organisms.

Nicotinic Acid.—The systemic employment of nicotinic acid (niacin)
been favorably reported upon for some time. Johnson (1945) said that he
been using this vitamin with eminent satisfaction for nearly four years
dose employed was 50 mg. three times daily for adults and 10 mg. and up
for children according to age. He said that a week's treatment usually su
to clear up the cases, the temperature subsiding however within forty-
to seventy-two hours.

Ascorbic Acid (Vitamin C).—Because of existing experimental evid
that low ascorbic acid levels might be associated with infections of this t
Field (1940) suggested that in critical situations 2.5 gm. of this substanc
administered intravenously in doses of 0.5 gm. spread out through twe
four to thirty-six hours; large amounts of the vitamin from natural sou
such as oranges and lemons should also be given. Kent (1943), writing of
treatment of Vincent's angina in soldiers during War II, said that asco
acid in large dosage should constitute a routine part of the treatment
advised 0.6 gm. daily for the first week and subsequently 0 3 gm daily.

VIRUS DYSENTERY

(*Epidemic Vomiting and Diarrhea; Acute Infectious Gastro-Enteritis; "*
testinal Influenza")

Increasingly in recent years there have been reported outbreaks of an
parently infectious and contagious acute gastro-intestinal malady usu
referred to colloquially as "intestinal flu." I have seen reports of these
demics in England and on the Continent as well as in the United Sta
Canada and Australia; most probably they occur elsewhere also. Usually
ut may persist at its p
f cases is often very hi
36, when it was thought
had more than 100,000 cases—I doubt the figure, but at any rate a good ma
people were sick with this malady at about the same time. Fortunately,
mortality is very low; indeed the primary mortality seems to be practica
nil. The characteristic symptoms are sudden onset of nausea, vomiting,
dominal cramps, watery diarrhea, slight headache and general aching, wea
ness, giddiness, and a general feeling and often appearance of a considera
degree of prostration. In various outbreaks one or other of the sympto
seems to predominate, for example, there is sometimes considerable vomiti
without diarrhea, while at other times abdominal cramps and profuse a
debilitating diarrhea are seen to the exclusion of most of the other symptom
Some patients are afebrile, others have grippal symptoms. In most instanc
the duration seems to be between two and five days, recovery occurri

quickly and without sequelae; relapses and second attacks, however, are of frequent occurrence.

[illegible]

and that it enters through the respiratory tract, and further that it is present in the oro-pharynx and stool but not in the blood. Most of the experimental attacks developed within one to four days with extremes of one to twenty-one days.

THERAPY

No specific therapy is at hand of course. In fact, since the condition is self-limited it does not seem to me sensible to attempt to do a great deal more than merely wait. A number of years ago, Wildman (1933) said that milder cathartics are not effective, that magnesium sulfate and mineral oil both [illegible]

in the severest cases the intravenous administration of 5 per cent dextrose effected striking improvement.

Greenthal (1936), discussing his experience of cases among children here in Milwaukee, said he knew of no measure which will relieve the severe vomiting in the beginning, but total abstinence from food and water for a few hours is probably advisable, however, if fluid is desired he allowed a few sips at a time of water, weak tea, carbonated beverages, cereal gruels and fruit juices, but not milk or broth. Heat to the abdomen is often very [illegible]

acute symptoms, Greenthal placed his children on a high carbohydrate diet —omitting milk, eggs, meats and soups and giving sugars and starches freely—and found that the diarrhea usually responded promptly to this regimen. In some cases he used the apple diet (see Index) with good results. Return to milk must be postponed for some time as it seems often to cause a relapse.

WHOOPING COUGH

(*Pertussis*)

Whooping cough is an acute infectious disease caused by *Hemophilus pertussis*. It is highly communicable and is therefore principally seen in very young children; nearly 50 per cent of cases are in infants under two years of age. There is no distinctive gross or microscopic pathology and the disease is therefore looked upon as one which remains local throughout its course. One attack is almost universally considered to confer life-long immunity, most observers looking upon the exceedingly rare second infections as really first infections in individuals who did not truly have whooping cough the "first" time. There are apparently a great many persons who possess a natural immunity to the disease.

There is an incubation period of three to twenty days and then another week or two during which the symptoms are those of coryza and bronchitis with cough. Gradually during the latter part of this period the paroxysmal natu[illegible]

The [illegible]

toms i[illegible]

a series of rapid, short, loud coughs, during which the tongue is protruded from the mouth, the eyes water and become injected, and the face is suffused or deeply cyanotic, and at the end of which there is a deep inspiration through the narrowed glottis, which causes the "whooping" sound (paroxysmal sneezing in rare instances may apparently replace coughing). In most cases there are several such attacks in quick succession, but they cease at once for the time being when a little mass of glairy mucus is brought up. There is often vomiting during the seizure and many times bleeding from the nose and other mucous membranes. The subconjunctival hemorrhages that occur are usually ascribed to the violence of the coughing. Altogether the attacks are a distressing thing to witness as well as to experience. Between paroxysms the patients, if old enough, are sufficiently undisturbed to engage in their customary amount of activity provided the case is of average severity. The "whooping" period usually lasts from three to six weeks but in many instances it is protracted for a much longer period; it subsides finally into a subacute bronchitis that often persists for many months In the city of Milwaukee during a ten-year period the average whooping cough mortality, as published by Fox and Knott (1944), was 0.25 per cent; but it is noteworthy [illegible] hospital

[illegible]

pneumonia accounts for most of the deaths, cardiac complications are rare. Nelson's (1939) thorough review indicated that neurological involvement occurs perhaps more frequently than has been thought. Meningeal or other hemorrhage due to violent coughing is a rare complication in children but one that is very dire in its results. Of course there is a greater likelihood of hemorrhage in adults, which makes us always apprehensive upon diagnosing whooping cough in one of advanced years. Surprisingly, whooping cough does not seem to be as harmful in active tuberculosis as one would *think* it should be. Lurie and Levy (1942) felt their study of 500 problem children justified the conclusion that whooping cough occurring early in *infancy* may lead to the development of severe psychopathologic conditions later in life.

The disease is transmissible throughout the prodromal period and up to and including the first part—but just how much of the first part, is not known

he has been whooping for four weeks, in England it seems that the period recommended is six weeks. The finding of the organism by the "cough-plate" method is considered a valuable aid in establishing diagnosis before the whoop appears, though Bullowa *et al.* (1944) and Silverthorne *et al.* (1945) concluded that the employment of the nasopharyngeal swab in combination with a cough-plate is of distinct advantage. During and after the second week there is nearly always a relative and absolute lymphocytosis.

Whooping cough was apparently unknown to the ancients nor is it men-

is very mild in the tropics.

THERAPY

There are two measures of paramount importance in the treatment of whooping cough. First, the child should be kept out of doors as much as possible, for in this way far better than any other will the number of paroxysms be reduced.

effect, I am

immersion o

diversion.

results in children of all ages.

Sedatives.—In mild cases, especially when the weather and other

Chloral hydrate	ʒi	4.0
Sodium bromide	ʒi	4.0
Syrup of orange to make	℥ij	60.0

Chloral hydrate alone in dosage of 5 to 10 grains (0.3 to 0.6 gm.) is satisfactorily given by rectum; Hoyne (1947) says that 1/2 to 3/4 grain (30 to 50 mg.) of seconal is also well employed by this route. Sauer (1946) says that a child of four may get some relief from a teaspoonful of the following mixture given before retiring and repeated if necessary once or twice during the night; he warns that it may produce a flush of the body:

Codeine sulfate	gr. iv	0.24
Saccharine	gr. ½	0.03
Tincture belladonna	♏xl	2.5
Elixir phenobarbital to make	℥iv	120.0

He also advises in severe cases the use of a retention enema of 25 per cent ether in olive oil given with a small catheter and bulb syringe every eight hours for a week or longer; the usual dose is two teaspoonfuls of the mixture for each year of age, the buttocks being held together for a few minutes to prevent expulsion. This mixture is inflammable of course but there is no danger of it causing necrosis. Epstein (1938) used the "elixir bromaurate," which is a uniform elixir of gold tribromide; the average dosage of the elixir is a teaspoonful every four hours for children, 2 teaspoonfuls for adults. *Barbiturates in combination with amidopyrine or acetanilid* have also been much employed; a capsule containing sodium amytal ½ grain (30 mg.) and acetanilid 2 grains (0.12 gm.) may be prescribed and the contents of ¼ to 1 such capsule according to age (one to seven years) may be given one-half hour before bedtime in jelly, followed by a hot drink; or the dose may be given one-half hour before mealtime and at midnight if necessary. Chlorbutanol (chloretone) is said also to be useful as a sedative here. Two grains (0.13 gm.) may be dissolved in a little whiskey, sweetened and *diluted to* [illegible] capsules [illegible]

[illegible] mg.) every two to three hours for an infant of six months, [illegible] gm.) at six hour—gradually increased to two hour—intervals for a youngster of two years.

Ephedrine and Synephrin.—Good results were reported a number of years ago with ephedrine hydrochloride. dosage, ¼ grain (15 mg.) to children over one year of age, ⅛ grain (8 mg) to those younger, in solution at bedtime, or night and morning, and occasionally three times daily. Some of the usual toxic symptoms are of course observed. Synephrin is used in doses of 1⅔ grains (0.1 gm.), scaled up or down for age; it is said to cause fewer side-effects than ephedrine.

Inhalants.—Occasionally a patient is benefited by the use of some such preparation for inhalation as is described in the discussion of the Common Cold; Epstein uses a teaspoonful of his elixir of gold tribromide in this way. However, these inhalants should not be used in children who are *running* in and out of doors during the colder months, for the mucous membrane seems to be especially susceptible to secondary infection for an hour or more after their use.

82.8 per cent of non-immunized susceptible control children came down with pertussis. The vaccine is administered subcutaneously in three doses of 1, 2 and 3 cc. at one-month intervals, first in the left deltoid region, then in the right deltoid region, and then in the left triceps region. Alum-precipitated vaccine is much preferred to fluid vaccine. Reactions of a local or systemic nature occur very occasionally and are not severe; Sauer and his associates have made a strong point of the fact that when using alum-precipitated vaccines the reactions can be minimized if the needle is directed distally during injection and the vaccine deposited deeply subcutaneously, and Sako *et al.* (1945) found that if, in evacuating the air from the syringe after it is filled, the vaccine is not allowed to come up so high in the needle as to cover the outside of the tip, the occurrence of sterile abscesses is entirely avoided Pertussis vaccine must be stored in a refrigerator at all times.

Most pediatricians are now beginning their immunizations shortly after the third month because at least half of the pertussis mortality has materialized before infants reach seven months. Sako (1947) presented data to show that immunization of young infants below three months of age is immunologically sound and highly effective if an alum-precipitated vaccine is used. He obtained positive agglutination titers in 92.1 per cent of infants below three months of age, 94.39 per cent in those three to six months, and 93.99 per cent in those six to twelve months. Of the infants below three months of age, 493 whose agglutinin titers were known and followed periodically every three to six months were exposed to pertussis within the household, 438 young non-immunized infants of comparable age whose agglutinin titers were negative and who were similarly followed periodically being exposed as controls; Sako himself made the diagnosis of pertussis clinically after a thorough examination and repeated observations and found that the incidence and severity of pertussis was far greater among the non-immunized (89.7 per cent) than in the immunized (13.2 per cent). His observation also supported a report of Miller *et al.* (1943) that, although immunity may exist in the absence of agglutinins, susceptibility is not present in the presence of agglutinins in titers of 1:320 or above. Also confirming other investigators he found that in young infants the height of antibody titer is reached in two to four months after completion of immunization with alum-precipitated vaccine, after which a plateau is maintained for three years or longer, the administration of a booster dose of 0.5 cc. eight to twelve months after the last inoculation effected a considerable rise in agglutinin titers in the vast majority of instances in his series. Waddell and L'Engle (1946) say it is their present custom to advise that immunization be started from six weeks to two months after birth; they believe that a booster dose at seven or eight months is probably not necessary though it may be an added measure of precaution. Sauer and Markley (1946), and Felton and Flosdorf (1946), feel that the pertussis agglutinogen skin test after immunization affords a simple method for differentiating the immune from the non-immune. Sauer and Markley find that the optimum time to perform the test is four or more months after the final dose of vaccine has been given and that the best time to read the skin test is twenty-four hours after it is performed; they feel that infants showing inadequate protection (an induration of 10 mm. or less in diameter) require a stimulating dose of vaccine at the time the skin test is read and that those giving a negative response require three doses of potent vaccine and a subsequent retest.

The studies of Kendrick *et al.* (1945) indicated that placental transfer of pertussis circulating antibodies occurs and that the higher the level in the mother the more nearly does the titer of the baby approach her own, however, ... infants to whooping cough is well known it is ... mothers is generally too low for effective ... Scadron (1946), continuing their earlier ... cent of women and about 85 per cent ... ng cough as demonstrated by lack of ... re propose that the mother be actively ... luring the last trimester of pregnancy with the aim of completing the p... hylaxis six weeks before term.

Combined Whooping Cough, Diphtheria and Tetanus Immunization.—This is discussed in the article on Tetanus.

Diphtheria Toxoid Alone.—Turnbull (1945) reported that in sixty-one children unquestionably exposed to whooping cough who were inoculated with diphtheria toxoid *alone* occurrence of whooping cough was prevented, in four others such prevention did not occur. I merely record Turnbull's observation here for the reason that it is extremely interesting.

...immune Human Serum.—Attempted passive immunization of in-

does develop in children who ha...

... (1946) says that when an exposure has been prolonged over twenty-

customary doses ... arms within a week.

YAWS

(Frambesia Tropica, Pian, Bubas)

Yaws is an infectious disease of the tropics that is acute in its onset but ... its course, the early manifestations being most frequently seen

greatest frequency on the ... around the anus and mouth, the scalp nearly always es... lesions ... Characteristically a "yaw" is a nodule varying in size from a pea to a large ... covered by a yellow or yellowish-brown crust from beneath which ... a thin fluid. If the crust is removed, there is revealed a raw surface ... fungoid granulations have given the name "frambesia" to the ... (frambesia

raspberry). Surrounding this lesion there is a dark area in natives, a reddish area in whites. The lymph glands often enlarge in groups but never become painful or suppurate. Mucous membrane lesions are very rare, perhaps they do not occur at all; but the mucocutaneous junctions are frequently involved. Occasionally there is a juxta-articular involvement resembling that of acute rheumatic fever, but it does not respond to the salicylates. The lesions, which are usually itchy but never painful or destructive, disappear in three to six

years, it is characterized by periostitis or osteitis, or by a gummatous type of nodule or ulceration, which on healing accounts for much later deformity. *Hackett (1946), as the result of a thorough study of yaws in Uganda, says* that the lesions of the secondary and tertiary types are never observed simultane-

between the tertiary lesions of yaws and those of syphilis. Gangosa, a very

which often before it subsides has

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deforming synostosis of the bridge of the nose.

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hat appear

when it is inoculated experimentally in both animals and man ... r clinically *and histopathologically from those of the latter disease.* In addition, the primary lesion is never venereal, the central nervous system is not attacked ... vascular system probably not, the disease is not congenitally

me time.

original

The opinion ...

home in Africa, since epidemics frequently broke out *on slave ships,* and the early planters in the West Indies quarantined the newly arrived slaves in an ... but according to Scott (1943), Oviedo, who accom-

aniola (*Haiti*). At the

the United States, or

Canada, and imported cases do not effect a spread in these lands. Indeed the occurrence of yaws in white men anywhere is extremely rare *unless the three* entities known in Ireland, Scotland and Scandinavia, respectively, as button-scurvy, sibbens and radesyge are accepted as yaws; Kinell's (1944), Lofgren's (1944), Rifkin's (1945) and Katzenstein's (1945) reports, each of an apparently undoubted cases of yaws in one of our white soldiers during War II, were of extreme interest. But the disease abounds in tropical Africa and Madagascar, in southern Formosa, in the Federated Malay States, in *French Indo-* China and in

rly in the

of Central

ppines, in

studies of

Viellards in

Ramsey among the hill tribes of Assam, ...

the mountains of northern Luzon, completely upset the previous belief that the disease is confined exclusively to lowlands, though in the highlands it does assume a somewhat different character.

To the historically inclined student, the controversy regarding the alleged identity of yaws and syphilis is of immense concern, but lack of space forbids me to enter into the matter here. The especially interested reader will find that the interesting treatise of Hudson (1946) will lead him into the voluminous literature.

In 1936, Kumm and Turner, of the Jamaica Yaws Commission, demonstrated the transmission of yaws from man to rabbit by an insect vector of the *Hippelates* genus, to what extent such insect transmission takes place from man to man under natural conditions is not yet known.

THERAPY

Penicillin.—In 1944, and again in 1945, Whitehill and Austrian reported the treatment with penicillin of a total of forty-one cases of primary and secondary yaws among Fijians, and in 1944 Findlay *et al.* in a preliminary communication reported the similar treatment of twenty-four cases in West Africa. Since the appearance of these papers numerous reports have appeared in the literature in which penicillin was used in smaller numbers of cases, and now there are two definitive fairly large-scale studies available. The British study is that of Hill *et al.* (1946), who treated 128 cases, fifteen being primary, ninety-six secondary and seventeen tertiary. The American study was that of [illegible]

Two hundred of the patients of Dwindelle *et al.* were hospitalized and given intramuscular injections of 40,000 units each every three hours round the clock for four days so that they received a total of 1,200,000 units. An additional 150 patients were treated on a two-day ambulatory basis with penicillin in beeswax and peanut-oil (Romansky formula), the two injections being spaced precisely twenty-four hours apart. Children six to twelve years old received 600,000 units; patients from thirteen to sixteen years of age 900,000 units; and those seventeen years old and over 1,200,000 units. A third group of 149 patients was treated on a one-day ambulatory basis with the Romansky formula; in this group children six to twelve years of age received 600,000 units in divided doses ten to twelve hours apart, patients from thirteen to sixteen years of age, 900,000 units at the same intervals, and those seventeen years old and over, 1,200,000 units at the same intervals.

In the penicillin-treated series of Dwindelle *et al.* (1946), described above, clinical improvement was observed to be very rapid and remarkable in the patients who were treated in hospital. Joint pains disappeared in twenty-four to forty-eight hours, plantar and palmar "crab" lesions became painless in forty-eight to seventy-two hours, both primary and secondary lesions began to dry up in twenty-four hours, and epithelium grew in from the periphery and completely covered most lesions in three or four days. The great majority of these patients who returned for observation one month after treatment showed complete healing of all lesions, though a few ulcerated primary lesions with secondary bacterial infections were still draining pus at this time, most of these healing spontaneously between the first and second month after treatment. The immediate clinical course in the patients treated on the ambu-

latory basis with the Romansky formula could not be followed, but when these patients were seen three months later at their first follow-up period they showed complete healing of all lesions in most instances, only three of the patients having ulcerated primary lesions which were still draining pus. It was felt that further observations would be necessary before a conception of relapse and reinfection rates could be formulated as a result of this study, but it seems significant that at the follow-up periods three and six months after treatment only three patients presented lesions suggestive of relapse. In one additional case it was thought that possibly reinfection had occurred. However, the serologic response lagged much behind the clinical and much behind what is observed in the treatment of early syphilis, for among the entire five hundred treated patients only eighteen had attained seronegativity at the three- or six-month follow-up period, though in almost all of the patients there occurred definite evidence of reduction in serologic titer after these intervals. In the hospitalized group of patients it was found that the darkfield examinations became negative in eight to twelve hours, by which time 120,000 to 160,000 units of penicillin had been administered. Sections made from biopsy material showed numerous spirochetes up to twelve hours but subsequently only occasional ones up to twenty-two hours and none thereafter. In summarizing their report, Dwindelle *et al.* said they felt that the therapeutic response to penicillin was just as good whether the agent was given during the four days of hospitalization or on a two- or a one-day ambulatory basis, in the latter two instances employing the beeswax-peanut oil preparation.

[illegible] cillin [illegible] nt of the bony lesions of tertiary yaws; of the seventeen cases in this category eleven gave immediate clinical remission of symptoms and almost complete disappearance of osseous signs within sixteen and a half days, four showed improvement, and two did not respond to treatment at all. In the two cases of goundou cure was not achieved but one of the patients had relief of pain and considerable decrease of swelling.

Arsenicals and Bismuth.—As long ago as 1926, Moss and his associates in Santo Domingo treated 1046 cases with neoarsphenamine. About one-half of the patients were reexamined from one to six weeks after treatment: of 362 patients given a single injection, only 19.8 per cent were cured or practically cured at this time, while of 169 given two injections, 51.5 per cent were cured or practically cured. The final conclusion, however, based upon another examination of 419 of the original 1046 patients, which was made nearly five years after their treatment, indicated that about 50 per cent of a miscellaneous series of yaws cases may be cured by one injection, that a second injection does not greatly raise this percentage, but that three injections very considerably increase the number of permanent clinical cures. More recent observations of others indicate that even more prolonged treatment than this is required to reduce the Wassermann reaction. Chambers (1944) reported that about 25 per cent of 411 yaws patients treated with six weekly injections of neoarsphenamine yielded negative Wassermann tests six months after treatment, about 45 per cent in twelve months, about 55 per cent in eighteen months, and about 68 per cent in twenty-four months. He reported similar results in 143 cases treated with four to six weekly injections of bismuth. Kinell (1944) apparently had no illusions about quick cures for in the case of the white seaman infected during War II, and previously referred to above, he

arranged for a complete course of ten intravenous injections of neoarsphenamine and the same number of bismuth subsalicylate injections intramuscularly, at first at four-day intervals and later at weekly intervals. In this case, as is usual in yaws, healing was in progress after two injections and when the patient was transferred twenty-one days after starting his treatment all the lesions were healed

Penicillin and Arsenicals.—Twenty patients in the series of Hill *et al.* (1946) were given penicillin together with an arsenical; the results suggested that penicillin in the acute stage followed by a more prolonged arsenical treatment might eventually prove to be the ideal therapy for ultimate and permanent cure, though it was recognized that further controlled observations would be required to establish this point It is indeed doubtful whether the accomplishment of complete cure is entirely desirable in a region where the possibility of reinfection constantly exists

Tartar Emetic and Potassium Iodide.—These two drugs are usually employed in the following formula, which is known everywhere in the tropics, specially of the eastern hemisphere, as "Castellani's Yaws Mixture":

Tartar emetic	gr j	0 065
Potassium iodide	ʒi	4 000
Sodium salicylate	gr x	0 650
Sodium bicarbonate	gr xv	1 000
Water (or chloroform water) to make	℥i	32 000

This amount (1 ounce of the mixture), diluted to three or four times the volume with water, is given three times daily to adults, counting everyone over fourteen years an adult, half doses are given to children of eight to fourteen, and one third or less to younger children Only the tartar emetic and potassium iodide are active against the causative organism, sodium salicylate being added to hasten the disappearance of the thick crusts and sodium bicarbonate in the hope of lessening the emetic properties of the mixture. Thi latter drug renders the preparation cloudy and inelegant, though it become clear when diluted with water at the time of administration. If emesis is pro duced, Castellani advised that the sodium bicarbonate be increased or th a small amount of an opiate be given before each dose. Europeans do not sta the full doses so well as do natives

The mixture is given for ten to fifteen days, discontinued for a week a then given again for ten to fifteen days The use of this formula is said to g very good results, though formerly neoarsphenamine, and now probably p lin, is preferred wherever it can be obtained.

YELLOW FEVER

Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever ar major infectious diseases that are not given consideration in this book f reason that the problems they pose lie nowadays almost entirely with province of public health authorities or other specialists of great expe

FLUKE INFESTATIONS

INTESTINAL FLUKES

Man is infested with intestinal flukes throughout a wide territory in the Far East: Japan, Korea, China, Indo-China, Thailand, India, British Malaya (Simmons *et al.*, 1944, said that most of the cases in the Settlements were imported), Netherlands Indies, the Philippines and some of the smaller Southwest Pacific Islands. Stoll (1947) estimates that there are about 10,000,000 infestations with *Fasciolopsis buski*, but that of the related form *Fasciola hepatica* there are probably no more than 100,000 human infestations In a very small proportion of the individuals harboring intestinal flukes there [illegible]

(a) the use of human excrement containing eggs for fertilizer; (b) the hatching of the eggs in the water and their penetration into the body of certain snails wherein they pass a portion of their life cycle; (c) eruption of metamorphosed forms from the snail and their encystment on aquatic plants; (d) the eating raw of contaminated water nuts; (e) maturation of the fluke in the human intestine where it sows its eggs.

THERAPY

[illegible] used of these agents, but McCoy and Chu (1937) reported the treatment of a large number of cases with hexylresorcinol, and Faust (1939) felt that possibly tetrachlorethylene would prove to be satisfactory. For details of the employment of these agents see the section on Worms.

LIVER FLUKES

Stoll (1947) estimates that there are about 19 million infestations with the liver fluke, *Clonorchis sinensis*, in Asia, and that there are 1 million infestations with the related *Opisthorchis felineus* in fisher folk in East Prussia, the Dnieper River basin, and northern Sverdlovsk in Asiatic U S S.R. Simmons *et al* (1944) said that *C. sinensis* infestations had never been reported from the Netherlands Indies This fluke passes a portion of its life in the body of a small snail and later penetrates into a certain species of small fish in whose muscles it becomes encysted; when this fish is eaten raw the parasite is introduced into the intestinal tract of man and the other animals which harbor it, whence its eggs finally issue to complete the vicious circle It seems possible for the majority of individuals to remain apparently healthy, though the bile ducts, and occasionally even the pancreas and duodenum, are considerably infested with

these flukes. In 367 consecutive autopsies on adult Chinese in Hong Kong, Uttley (1935) found clonorchis present in fifty-two instances, but in no case had the fluke been the cause of death. When symptoms arise they are the following: gastro-intestinal pain and tenderness, nose-bleed, jaundice and bloody diarrhea; in severe cases edema, ascites, anemia and death from cachexia.

THERAPY

The anthelmintic drugs have been usually considered a complete failure in the treatment of liver fluke infestation. Kouri and Valverde (1935) reported the successful use of emetine in two cases (see methods of employing this drug in Amebiasis). Shattuck (1924) used tartar emetic (as in Leishmaniasis) and the arsphenamines in six asymptomatic cases, and wrote, "The facts seem to indicate, first, that both tartar emetic and arsphenamines are somewhat poisonous to clonorchis; and second, that it may be advantageous to give them in successive courses"

Kinugasa (1939) found fuadin (see Bilharziasis below) superior. Faust (1939) said that gentian violet, crystal violet, or methyl violet may be helpful; oral dosage in enteric-coated pills is 30 mg. every other day and not to exceed a total of 300 mg./kg. Manson-Bahr (1940) said that spectacular results sometimes follow the duodenal tube bile drainage that seems often to be resorted to in Korea.

LUNG FLUKES

The fluke, *Paragonimus westermanii*, infests dogs, cats, pigs, rodents and the larger carnivorous animals over a wide range. It is also established as a [illegible]

[illegible]

slight fever, cough, expectoration of brownish-yellow tenacious sputum often containing blood, particularly if these symptoms are accompanied by a history of thrombophlebitis of the leg

THERAPY

So far as I am aware no satisfactory treatment has been developed for this malady. To and Ko (1935) reported the partially successful use, in four cases, of 5 per cent carpaine hydrochloride in normal saline, injecting subcutaneously. The total quantities used were respectively 0.3 gm. over six days; 1.1 gm. over twenty-three days; 0.5 gm. over ten days; and 0.9 gm. over thirty

thiazine and lipiodol injections into the bronchial tree in their cases but they were not impressed by the results obtained.

BLOOD FLUKES

(Bilharziasis, Schistosomiasis)

... who first wrote of it in 1852

is

an

the urine and feces of infested men or animals; in fresh water, motile larvae develop and enter certain specific snails; after about six weeks another form of larvae leave the snails and move about very actively in the water, it is these latter larvae that pierce the skin or buccal mucous membrane of persons or animals during bathing or drinking and set up the disease. The venous system is quickly entered and in the larger portal vessels the flukes mature and become paired. In pairs (male and female) they then travel toward the periphery and become lodged in the submucosal veins of the intestines and bladder, ... more rarely the cerebral cor-

... d as sites for these

... ivolvement of the central nervous system is more frequent in *S. japonica* than in *S. mansoni* and *S. haematobium* cases. The pathologic reactions consist in a cellular response to the general toxemia and a local inflammatory reaction to the presence of the aggregations of eggs; chronic inflammatory changes lead ultimately to fibrosis, especially in the liver and colon; according to Koppisch (1943) there is usually present but little evidence of acute colitis in the late stage. Bercovitz *et al* (1944) described an interesting group of young Puerto Rican patients who were infected with the parasite and in whom there were definite pathologic findings in the rectal mucosa but no other clinical symptoms; in a later report (1945) on this group it was said that the blood picture was not observed to be significantly altered from the normal.

When the larvae penetrate the skin there occurs in some individuals for a ... be termed

... pear:

... aria,

... izing

eosinophilia, anorexia, and possibly abdominal pain and tenderness over the liver region. The increase in the mass of the intestines, plus the enlargement of the liver and spleen which are passively congested, pushes the diaphragm upwards and decreases the intrathoracic volume. In late chronic cases ascites often develops. This syndrome, which is known in Japan as

Katayama disease, is not recognized elsewhere in the world as often as it should be. The symptoms due to the local processes in the bladder and intestine usually do not appear until another three to thirty months have elapsed. In the intestinal cases the symptoms are not clear cut but there are usually recurrent attacks of bloody dysentery and colicky pain and tenesmus; there are palpable papillomata of the rectum, more particularly in Oriental cases, [illegible]

There is a tendency for malignant growths to engraft themselves upon these local lesions. Cardiovascular and pulmonary involvement in bilharziasis has been described (Clark and Graef, 1935, Shaw and Ghareeb, 1938). The diagnosis of schistosomiasis by methods of microscopical examination of feces for the eggs of the schistosome worms is a very costly procedure and a difficult and not entirely satisfactory one; Hollands and Palmer (1946) have found a rectal crypt aspiration technique a more reliable and time-saving method, and Hernandez-Morales and Maldonado (1946) have successfully employed rectal mucosa biopsy Methods employing humoral responses of the body, such as intradermal, flocculation, precipitin and complement-fixation tests have been employed as diagnostic aids, but none of these prove that the parasite is actually present in the host at the time the test is positive and they are furthermore open to objections on the basis of bias in the reading (particularly is this true in the case of the skin test).

[illegible]

[illegible]

War II in 1672 instances.

Spontaneous cure is undoubtedly effected in some cases of bilharziasis after a variable length of time, and it is often stated that ova cease to be passed in the urine and feces of an individual after three years of residence outside an endemic center. However, in Cutler's review of the subject a number of years ago it was clearly shown that both *clinical and laboratory evidences of the* disease may persist for ten or more years of consecutive residence in a nonbilharzial country.

THERAPY

Tartar Emetic.—It is only since 1918, when Christopherson introduced the use of tartar emetic, that we have been able to speak of having a specific [illegible]

reinfestation has taken place, the ova will not reappear until three or four months have elapsed. Alves and Blair (1946) reported the very satisfactory employment of intensive antimony therapy, principally in *S. haematobium* cases, in Southern [illegible] (*they* call this almo[illegible] total daily dosage [illegible] noon and 8 P.M. on two successive days. The solution used contained 1 grain (60 mg.) per cc. made up with 5 per cent glucose saline solution to 10 cc; this was injected intravenously using a 23-gauge needle and injecting during a minimum time of five minutes. In the series of 110 patients it was not necessary to discontinue or modify the treatment in any case on account of a severe reaction to the drug, bu[illegible] in many of the patients on the day after [illegible] full military duty within [illegible] eggs were found *in any case immediately after treatment* or two months and three months after treatment in the cases followed up, and in thirty-nine of fifty-three cases the skin test had become negative in two months, in six of the remaining fourteen cases it became negative in another three months. Alves (1946) later reported a still more intensive type of employment of tartar emetic, treating three groups of patients with different dosage schemes, em[illegible] of tartar [illegible]

(0.16 gm.) at four-hour intervals, and (c) eight grains [illegible] of two grains (0.13 gm.) at three-hour intervals. The treatment thus occupied only one day; it was said that no marked reactions occurred and that there was not any obvious difference between the groups receiving the different doses. Urines and stools of every patient were examined two weeks and four weeks *after treatment* and in none of them were living eggs found, but admit-

tedly the follow-up was not long enough at the time of the report to assure the [illegible]

Mason *et al.* (1946), studying 481 cases of *S. japonica* infestation on Leyte Island, used a 0.5 per cent solution of tartar emetic in 5 per cent dextrose in [illegible]

Blair) solution rather than a 2 to 6 per cent solution as was formerly done, has enabled patients to take the drug with much greater ease and fewer reactions. However, Faust (1946) says that one should bear in mind the fact that a few people are intolerant to antimony and have uncontrollable bronchial spasm when tartar emetic is injected intravenously and that some have uncon- [illegible]

of Tarr (1946) indicated that the electrocardiographic changes induced by antimony represent but a transient side action of the drug not indicative of cardiac damage or serious impairment of cardiac function. There is further mention of antimony toxicity in the article on Leishmaniasis.

[illegible]

cases in a 6.3 per cent solution. The initial dose was 1.5 cc. followed by one of 3.5 cc. on the next day and one of 5.0 cc. of the drug after that; thereafter 5 cc. was injected every other day until a total of 65 cc. had been given. Apparent cure (negative stools) was accomplished in only 18 per cent of cases as against the same result in 81 per cent of cases in which tartar emetic was used. Winkenwerder *et al.* (1946), and Rodriguez-Molina and Shwachman (1947), also found fuadin a not very efficient drug, the latter in *S. mansoni* cases. Faust (1946) says that it has a relapse record of 70 per cent in *S. japonica* cases even when used in larger doses than ordinarily recommended whereas tartar emetic, administered as a 0.5 per cent solution in a total approximating the same amount of antimony, has a relapse record of only 16 per cent.

Anthiomaline.—Mills (1946) found that this antimonial compound (and indeed fuadin) was effectively employed in his eighty-six cases of *S. haemato-* [illegible]

it best to give a dosage of 3 cc every other day for a total dosage varying from 20 to 48 cc. No serious toxic reactions were observed and in every instance the stools were free of the schistosome before the treatment was completed. In 89 per cent of the patients no relapses had occurred during follow-up periods of from two and a half to nine months.

PROPHYLAXIS

Of course no drinking of, or wading or bathing in, fresh water in areas of bilharzial endemicity should be indulged in. Suspected drinking water may be rendered safe for use by storing it in snail-free tanks for seventy-two hours, for most of the larvae perish unless they enter the human host within a relatively short time after they leave the snail. Sandbed filtration is not effective against them but Berkefeld and Pasteur-Chamberland filters hold them back. It is said that in endemic areas application of sufficient chlorine to water used for bathing, drinking or laundry purposes to provide one part per million residual at the end of thirty minutes affords protection against *S. japonica* larvae as well as against those of *S. mansoni* (Bull. U.S. Army Med. Dept, 89, 13, 1945); this is considerably more than the average chlorination here in the United States, for in Milwaukee the chlorine content of the water leaving the plant for distribution is held between 0.35 and 0.4 parts per million.

SCHISTOSOME DERMATITIS

("*Swimmer's Itch*")

Waders, bathers and swimmers in the lakes of the north-central part of the United States frequently complain of a severe form of itching that attacks them after

trade has

disturbance

Not every

the minority; children are the most frequent and most severe victims. In a typical case the itch is fully developed in half to one hour after leaving the

days, the lesions often requiring several weeks to fade out. In 1928, Johns Hopkins University, determined this malady to be due to penetration of the skin by the free-swimming larval forms of certain schistosomes; Cort subsequently contributed much to further the understanding of the subject, and in more recent years Brackett and his associates considerably added to our knowledge. Of a number of schistosomes known to be the active agents in this country, it seems that *Cercaria stagnicolae* is the principal offender. What

birds), they develop into embryos that enter the bodies of snails, ... about

veins so that the eggs may be deposited in the water ... but if a human being is in the water and in the path of these cercariae they strive ... to the itching and the ... that the organisms ... probably do not reach

the deeper tissues, so there is no warrant in present knowledge for the fear that a systemic form of schistosomal infection will result from one of these attacks.

THERAPY

Ridding lakes and bathing beaches of snails by the use of copper sulfate or carbonate or formaldehyde additions to the water has not proved an entirely practicable measure as yet Brackett (1939) showed that the best protection against an attack is to rub down the body vigorously with a towel after leaving the water—not soon after leaving but at once, for there is evidence that most of the penetration takes place when evaporation begins, for this reason children who are paddling in and out of the water frequently are the most severely affected

Antipruritic lotions (see Index) are usually the only agents indicated in treatment

WORM INFESTATIONS

TAPEWORMS

The principal tapeworms infesting man are *Taenia saginata*, *T. soliun* *Hymenolepis nana* and *Diphyllobothrium latum* (*Bothriocephalus latus*). Th following have also been occasionally recorded: *Hymenolepis diminuta*, *H lanceolata*, *Diphyllobothrium cordatum*, *Diphyllobothrium ranarum*, *Dipylidiur caninum*, *Diplogonoporus grandis*, and *Davainea madagascariensis*. In 194 Chandler described the first recognized infestation of man with *Mesocestoide variabilis*. Stoll (1947) estimates about 39 million infestations with *T. saginat* throughout the world, mostly in Africa and Russia, and about 3 million infes tations with *T. solium*, nearly half of the latter being in Asia He says tha there are about 20 million *H nana* infestations, two-thirds of them being i Asia *D. latum* shows a world total of about 10 million cases, about 3 millio of which are in the Baltic littoral, northern Russia and Asiatic Russia.

Taenia saginata, the beef tapeworm, and *Hymenolepis nana* are the tw most common tapeworms in the United States and Canada. *T. saginata* attaches itself in the upper part of the intestinal tract of man only, usually but one worm being present at a time. The larvae encyst in the muscular tissues of cattle, and it is the eating of these tissues raw or insufficiently cooked that introduces the parasite into its human host. If beef is solidly frozen the larvae die within six days and they die also in ordinary cold storage of three weeks' duration, but in the latter case their death is due not to the low temperature but to the fact that they are unable to survive the death of their host for a longer period.

... the larval form It is ... al and is ... *asters* as well as man and there is some presumptive evidence that the rat flea may act as intermediate host by harboring the larval stage of the worm.

... tissues of pigs and passes ... eaten raw or insuf- ... man consumption by cold storage or even by freezing. The larvae are also harbored *in deer, bears, monkeys, dogs and cats. Man can become* infested by eating foods contaminated by another infested individual, as it does not seem necessary for the larval stage to be passed in another animal; he may also reinfest him- self if a ripe proglottis happens to pass upward into the stomach, where it will liberate its ova. The larval form, *Cysticercus cellulosae*, sometimes enters the ... gives rise to *the entity* ... oms; death of such ... the toxic products *of their dissolution, may give rise to symptoms* indistinguishable from those of idiopathic epilepsy. The adult worm develops only in the intestinal tract. Multiplicity of worms is not the rule but the occurrence of more than one is more frequent than with the beef tapeworm.

Diphyllobothrium latum is the broad or fish tapeworm. The eggs of this tapeworm hatch in water and the larvae enter the bodies of certain small

the intestinal tract of man, dogs, pigs, cats, foxes and perhaps all other fish-eating animals; they are very long-lived, a case being on record in which one of these worms was harbored for sixteen years. It is therefore not remarkable that the western portion of the Great Lakes region of the United States and Canada, so largely populated by immigrants from the Baltic region, has

diction. At least four species of food fishes have been inculpated. It seems that these are taken commercially in only very small amounts from the contaminated portion of Lake Superior, but Vergeer believed that infestation would

children in subtropical Florida; these cases were thought to have been almost indubitably acquired through the eating of improperly cooked fish native to that region.

Tapeworm infestation is said to be manifested by any or all of the following symptoms: abnormal appetite, picking of the nose and scratching of the anus, restlessness at night and a large array of nervous symptoms by day, vertigo and a sinking sensation, anemia, a sensation of weight in the epigastrium, attacks of colicky abdominal pain, nausea and vomiting, and ova in the stools. The ova can always be found if the microscopist is an expert and is not satisfied with a single examination. In the case of *T. saginata*, segments often wander out of the anus when the patient is not at stool so that he soon becomes aware of his malady, segments of the other members of the group are usually passed unnoticed with the feces. In individuals harboring *D. latum*, the blood picture sometimes closely resembles that of pernicious anemia, but it would seem from the studies of Von Bonsdorff (1943) and Tötterman (1944) that the cause of this type of anemia in these cases is the taking of a dietary inadequate in Castle's extrinsic factor; Helander (1945) finds the hydrochloride acid secretion in the stomach and the production of intrinsic factor as good in these patients as in normal individuals. It cannot be too strongly impressed upon the reader that his patient may harbor any of the tapeworms and manifest no symptoms whatever. To examine the stools of any individual whose symptoms are of a vague nature is good practice.

THERAPY

In the treatment of a patient infested with any of the tapeworms several

said that castor oil does *not* increase the toxicity of aspidium). Second, the

sometimes occur; therefore the patient should be caused to stay quietly in bed throughout the course of the treatment. Third, the dose of the drug must be followed by another saline purge in order to sweep out the worm and the remnants of the drug. Fourth, careful search must be made for the head. If the treatment has been successful it will nearly always be found *if properly searched for by the physician himself*, though it sometime is discharged separately within the next few days, or it may be digested and not discharged at all; the latter occurrence is probably very rare. In any case, if ova continue to be passed in indication that the treatment has failed, it should not be repeated in less than one month and in weakly individuals not for a much longer time.

The toxicology of vermifuges is presented at the end of this section. It is probably well not to employ any of these drugs during pregnancy—pumpkin seeds are the exception as these seem to be harmless under any conditions.

Aspidium (Male Fern).—This agent is probably more often effective against tapeworm than any of the other anthelmintics. The usual dose of the oleoresin of aspidium as gauged for children is 7½ grains (0.5 gm.) per year of age, ... in an adult it is doubtfully ... e substance is extremely dis- ... following prescription, which ... any:

℞	Oleoresin of aspidium	gr xl	2.6
	Fluidextract of glycyrrhiza	ʒss	10.0
	Syrup of orange flowers	ʒv	20.0
	Peppermint water to make	℥ij	60.0
	Label. To be taken in 1 dose.		

Magath and Brown of the Mayo Clinic, use the following emulsion for an adult:

Oleoresin of aspidium	ʒiss	6.0
Powdered acacia	ʒij	8.0
Water to make	℥ij	60.0

They direct that the patient should omit luncheon and supper on the day preceding treatment, though black coffee, tea and water are allowed. At 6 P.M. a dose of magnesium sulfate is taken and this is repeated at 6 A.M. next day. Then, without breakfast and after the bowels have moved, half the dose of the drug is given; one hour later, the other half. After two more hours, another dose of magnesium sulfate, and two hours after this a large soapsuds enema. The stool is then passed into a container, but the toilet paper should ... of the ... [by ... hen ... the

head ... ly with 30 cc. ... gle case; the ... in the second

portion of the duodenum but the vomitus was saved, kept warm, and later reintroduced with the addition of more magnesium sulfate solution. The worm was expelled with head intact.

Pumpkin Seeds. (Pepo).—Pumpkin seeds not over a year old are used. [illegible] results; in short there is apparently no harm in giving all the patient will accept. The seeds are reduced to a paste in a mortar and rubbed up with sugar and perhaps a little honey It is said that children like this mixture, to which a little milk may be added if desired. Goriacheva (1941) used the pumpkin seed treatment in twenty-three children aged six to twelve years and the number of worms expelled was insignificant; eggs reappeared in the feces of twenty-one of the children within two weeks to three months.

[illegible] Half this dose is sufficient for children.

Pelletierine Tannate.—This is a mixture of several alkaloids of the above bark and is easier to give since the dose is small, being only 4 grains (0.25 gm), and it can be easily suspended in simple syrup. This is considered by many practitioners to be the most surely effective of all the vermifuges available for the treatment of tapeworm, but it is too toxic for any but very robust individuals and it should perhaps never be given to children.

Carbon Tetrachloride.—Sandground (1938) reported the successful use of this drug in a small series of cases (see methods in Hookworm), and Mackie (1939) and Mukerji and Maplestone (1943) also commended it; there had been earlier favorable reports but the drug has not been widely adopted for use in tapeworm infestation.

[illegible] *H. nana* infestations with acranil, an acridine derivative closely related to quinacrine (atabrine). The night before the administration of the drug the children were given calomel and then on the following morning acranil was given on an empty stomach in doses of 1½ to 7½ grains (0.1 to 0.5 gm.) accord- [illegible] three to sixty years, thirty-four were cured by a single treatment, three after two doses and one after three doses; three were not cured and six were still under observation at the time of writing and the effects upon three could not

be followed. Thus out of forty-one subjects 92.6 per cent were cured, test of cure being either the finding of the head, which was unusual, or subsequent clinical examination and observation of feces. Seven of the patients exhibited nausea and vomiting, abdominal pains, diarrhea and yellow discoloration of the skin; Niño suggested that introduction of the drug through the duodenal tube might avoid some of these reactions.

Quinine.—Sokolovski (1933) reported success in promoting expulsion of [illegible]

HYDATID DISEASE

(*Echinococcus Disease*)

Taenia echinococcus is a small tapeworm of the dog and his congeners, the fox, the jackal, the wolf, etc.; more rarely it infests other carnivorous animals. The ova are spread in the feces of the infested dog and are also deposited upon the objects he licks with his tongue. Grass eating animals such as cattle, sheep, pigs, deer, moose take up the ova with their food and act as secondary hosts for the parasite; when the dog eats the uncooked viscera of these animals he acquires the larval form of the worm, and so the vicious circle is perpetuated. Man may acquire the ova by too intimate association with infested dogs, or much more rarely by ingesting uncooked contaminated vegetables or drinking water. The embryo is freed by the digestive juices in the stomach, passes down the intestine, is taken up by the portal vein and passes to the internal organs, where the larvae in developing cause the condition known as echinococcus disease. The liver is the stopping place for the parasite in about 75 per cent of the cases, the lung in about 9 per cent and all the other organs and tissues combined in about 16 per cent. Barnett (1945) stressed the fact that primary peritoneal cysts are rare. Brain cysts, when primary, nearly always occur in childhood, such a cyst in an adult being probably secondary to cyst of the heart. Fortunately localization of echinococcus in bony structures is rare, for surgical treatment is often unsatisfactory and can easily lead to dispersion of the scolices.

Since a pathologic description of a hydatid cyst is not within the province of this book, it must suffice here to say that the ultimate form of this cyst is a brood capsule containing, if not secondarily infected, a crystal-clear fluid and a great many scolices or rudimentary worm heads; there are usually quite similar cysts within the cavity of this primary cyst, and even these secondary cysts may themselves contain cysts. The symptoms are those of a characteristic tumor in an individual not otherwise greatly affected in health. X-ray, the complement deviation and the intradermal tests are of assistance in making the diagnosis, though none of these tests seems to be infallible. Of course if rupture takes place into any of the body cavities, the symptoms of shock and collapse are to be expected. After such a rupture a new a crop of cysts may develop in great number. If a cyst becomes infected, which often takes place through the bile ducts apparently, the picture of sepsis plus jaundice and often urticaria is superimposed. In regions where the disease is frequently encoun-

tered it is not often confused with other entities, such as malignancy or tuberculosis, but where hydatid disease is unusual the diagnosis is rarely made outside the operating or autopsy room.

At the present time echinococcus disease is most prevalent in Australia, New Zealand, the Argentine, Chile, Uruguay, Cape Colony, southern Brazil, Mecklenburg, Pomerania, Bavaria, Switzerland, Iraq, Iran, Austria, Jugoslavia, Hungary, Dalmatia, Bulgaria, Greece, Turkey, Eygpt, Russia, Siberia, Morocco, Palestine, Syria, Roumania, France, Italy, Wales and Iceland. For most of the world there are no reliable figures available. Maplestone (1933) believed that the incidence is higher in India than the literature would indicate. Haddad and Khairallah (1940) said that in their hospital in Syria one out of every one hundred and fifty patients had hydatid disease. Dungal (1946) says that while in Iceland there is still a very high infestation rate among the oldest age groups that are a remnant of the old conditions when the population was heavily parasitized, the present young generation is practically free from echinococcus disease. Magath (1939) reported that less than 500 cases had been recorded in the American literature from 1880 to 1938 and that of these fewer than twenty-five were in natives of this country and Canada; however, Hudson (1945) found three cases of calcified cyst of the liver in native Georgians within a short period of time and felt that this fact together with the established presence of echinococcus disease in hogs and cattle in Georgia—he found hydatid cysts of the liver in hogs and cattle in Georgia—suggests the possibility that the disease may not be as rare as it is usually considered to be in native-born Americans. In 1946, Magath predicted that within ten years of the end of War II we could expect to see many cases because of the numerous dogs in and about camps and serving as pets and mascots during the war.

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I am unable to find any satisfactory evidence that either drugs or biologicals are of the least value in the treatment of hydatid disease. Direct surgical attack, on the other hand, is often productive of the most excellent results. Barnett (1945) says that lung cysts in the young should be given the chance of spontaneous cure unless there are indications of sepsis and toxemia; he points out the danger of tapping which apparently, according to Scott (1945) lies in the fact that the cyst wall may rip and flood the lung with fluid. In bone cases removal of the entire diseased area may remove the disease but is certainly a mutilating procedure. Theoretically, the use of the x-ray would be indicated, but the work of Dévé conclusively showed that its employment is impractical for the reason that the scolices within the cysts succumb only to a dose of the ray that would be highly injurious to the tissues of the patient.

PROPHYLAXIS

In Iceland, which has been a great sheep-raising country for over a thousand years, hydatid disease reached its highest incidence about 1867, since which time a remarkable drop has occurred. Ofeigsson (1937) listed the following prophylactic measures as having effected this change (1) the decrease in poverty with increased freedom from foreign rule and especially since Iceland became a free country, (2) better hygiene, (3) Krabbe's discovery in 1863 of the life cycle of the echinococcus, (4) the rapid spread of the knowledge of this discovery among Icelandic doctors and laymen, who realized the importance of breaking the life cycle of the parasite; (5) more and better doctors;

(6) laws forbidding all unnecessary dogs, resulting in a great reduction of their number; (7) *a quarantine for two days*, once or twice a year, of all dogs during which they are treated with baths and suitable drugs; (8) warnings to people *against too much petting* of their dogs and careful washing of their hands after touching them; (9) laws forbidding farmers to slaughter their sheep on their *farms* and permitting only authorized slaughter houses which are supervised

infection had not yet begun to wane in New Zealand.

THE COMMON ROUNDWORM

Ascaris lumbricoides is the intestinal worm most commonly infesting man; Stoll (1947) estimates that there are 644 million infestations in the whole world. The worm is quite ubiquitous, but in cool climates is encountered

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THERAPY

Hexylresorcinol.—Practically all observers are in agreement with Einhorn *et al.* (1945), in Panama, who found hexylresorcinol the safest, most efficient and certainly the easiest of the anthelmintics to administer; they said that frequently it was surprising to see how soon after beginning treatment the children began to look brighter, became more energetic and developed ravenous appetites Smillie (1942) said that a single administration will remove about 80 per cent of the worms. However, the stools must be examined at monthly intervals for three months and treatment given again if ova are found. Hexylresorcinol is used in the following dosage: 6 grains (0 4 gm.) to very young children, 10 to 12 grains (0.6 to 0.8 gm.) to those from six to twelve years; 15 grains (1 0 gm.) above twelve years. The best method is to give the drug early in the morning on an empty stomach, followed within an hour to an hour and a half by a saline cathartic, and then no food to be taken until noon. Often there have been complaints of slight burning gastric irritation and occasionally a patient vomits, but no reactions of more serious moment have been recorded. The drug was first made available in crystalline form in hard gelatin capsules but it was said that a reaction often occurred between the active agent and the gelatin (particularly in warm, moist climates); an occasional superficial burn of the mucosa of the mouth was also seen if children chewed the capsules. The first substitute for these capsules was the familiar sugar-coated pill, but as this can also be chewed a new type of capsule, "crystoid anthelmintic," that is said to be very difficult to chew has been made available.

Oil of Chenopodium.—Oil of chenopodium won a place for itself in roundworm therapy on the basis of efficacy but did not hold it long after hexylresorcinol was made available in a satisfactory form for administration (see Hook- [illegible]

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Santonin.—This is the oldest of the remedies for roundworm infestation It is insoluble outside the intestinal tract and practically tasteless and therefore may be easily administered to children by incorporating the dose with a little sugar. Calomel, given to lessen absorption and to sweep out the stunned worms, may conveniently be added to this mixture; the commercial tablets [illegible]

[illegible] of age, the drug being given two or three days in succession and the treatment repeated if necessary after a lapse of ten days. Preparatory semi-starvation is not so necessary with this drug as with some others; it may be given several [illegible]

[illegible] the maximum adult dose I have so often recounted to my students an aston-

(6) laws forbidding all unnecessary dogs, *resulting in* a great reduction of their [illegible]

touching them; (9) laws forbidding farmers to slaughter *their sheep* on their farms and permitting only authorized slaughter houses which are supervised *rigidly*; (10) *inspection* of all meat by veterinary surgeons; and (11) burning or burying of all infected organs of sheep and cattle. According to Barnett, in 1941, in spite of a similarly intensive preventive campaign the incidence of *infection* had not yet begun to wane in New Zealand.

THE COMMON ROUNDWORM

Ascaris lumbricoides is the intestinal worm most commonly infesting man; Stoll (1947) estimates that there are 644 million infestations in the whole world. The worm is quite ubiquitous, but in cool climates is encountered principally in children. In the tropics, however, and in many regions of poor *sanitation in northern latitudes, the incidence is very much higher* and the worm occurs in individuals of all ages. Fifteen of Swartzwelder's (1946) 202 patients in New Orleans were over thirty years of age. In China and other countries where the custom of employing night-soil in vegetable *gardens* prevails this worm is harbored with a frequency astonishing to practitioners in Europe and North America; in Egypt, average prevalence in the Nile delta is as high as 80 per cent according to Scott (1939); Fernando and Balasingham (1943) estimated that two-thirds of the population of Ceylon are infested.

This parasite needs no intermediate host for its full development. When the egg is swallowed by man it hatches in the small intestine, migrates to the liver and then to the lungs; from the latter situation it passes up the trachea and down the esophagus and through the stomach to settle down to maturity in the small intestine. An individual usually harbors from four to six of the adult parasites but sometimes the number is much greater than this. In Swartzwelder's *(1946) 202 cases the most common chief complaints,* symptoms or physical findings in order of their frequency of occurrence were the following abdominal pain or discomfort, passing of ascarids prior to treatment (by anus, mouth or nose), vomiting, abdominal or epigastric tenderness, fever, constipation, abdominal distention, cough or cold, nausea, headache and diarrhea Convulsions, abnormal pulmonary conditions, anorexia, loss of weight, weakness, malaise, restlessness, abdominal rigidity, palpable abdominal mass, dyspepsia and dyspnea ranked next in order of frequency. In about one-third of the cases the symptoms were evident for a week or less prior to admission. When an individual harboring roundworms develops fever, as during the course of one of the infectious diseases, the worms seem to be disturbed and show some tendency to wander from the intestine into the stomach, esophagus, upper air passages, bile ducts, or even more distant parts of the body. Remote [illegible] complicat- [illegible] ount [illegible] ated [illegible] reat- [illegible] tely [illegible] contraindicated.

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Oil of Chenopodium.—Oil of chenopodium won a place for itself in roundworm therapy on the basis of efficacy but did not hold it long after hexylresorcinol was made available in a satisfactory form for administration (see Hookworm for methods of using oil of chenopodium), *i e*, hexylresorcinol is preferred in private practice but in mass administrations in field work the drug is much too expensive and there oil of chenopodium has still to be preferred. Smillie (1942), while admitting the potentially greater toxicity of oil of chenopodium, nevertheless stated it to be the superior anthelmintic since one administration of it removes 90 to 95 per cent of the worms instead of the 80 per cent removed by a single administration of hexylresorcinol.

Santonin.—This is the oldest of the remedies for roundworm infestation. It is insoluble outside the intestinal tract and practically tasteless and therefore may be easily administered to children by incorporating the dose with a little sugar. Calomel, given to lessen absorption and to sweep out the stunned worms, may conveniently be added to this mixture; the commercial tablets containing ½ grain (30 mg) of the drug and an equal quantity of calomel are so pleasing to children that they will eat too many of them if the supply is not carefully guarded. Santonin dosage for children is 1/6 grain (10 mg) per year of age, the drug being given two or three days in succession and the treatment repeated if necessary after a lapse of ten days Preparatory semi-starvation

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neum causes intense itching; in the process of scratching many of the females are crushed and their eggs liberated; the hands, contaminated with eggs, are ultimately carried to the mouth, and the whole circle is completed with the reinfestation which thus takes place Recent studies have also shown that viable eggs contaminate the lower objects in rooms also, such as furniture legs, rugs, window ledges, etc., Cram (1943) even found the eggs at all levels from floor to ceiling Severe anal pruritus is the only definite symptom of pinworms, though it is perhaps not entirely incorrect to ascribe some of the nervous disturbances of young children, especially those with erotic manifestations,

nutrition, insomnia, nervousness, enuresis and pruritus ani; Cram (1943) agreed in the main except for the matter of the incidence of enuresis Some observers believe that the worm is responsible, directly or indirectly, for many cases of appendicitis, but this is certainly not proved though the worms are many times found in that appendage when it is removed Diagnosis is made

phane; this is stroked outward over the perianal mucosa and the cellophane square is then transferred to a glass slide and examined under the microscope), or the use of scotch cellulose tape applied to a wooden applicator in much the same way. A single NIH examination is from 40 to 50 per cent efficient; many observers have confirmed the finding of Sawitz *et al* (1939) that seven such swabbings, on alternate mornings, will detect practically 100 per cent of infestations. It is claimed by Schüffner and Swellengrebel (1943) that their pestle method is far more speedy and reliable than the swab methods

THERAPY

anus to mouth by contaminated fingers could be *absolutely* prevented for a period of two to three weeks, it was thought that the infestation would be cured Now, however, with some investigators maintaining that the cycle may be several months in length and others that in some instances the eggs may be laid within the bowel and the cycle be completed there (the evidence for this latter contention is unimpressive), the hope of curing the patient with hygienic measures rigidly maintained during the period covered by one

ture, etc.

The treatment should begin with a full bath with soap and water, special attention being paid to the anal region After this the anal region and the perineum are to be anointed with an ointment composed of 2 per cent of ammoniated mercury in equal parts of lanolin and petrolatum, a pad of cotton applied, and the child clothed in heavy drawers that are closed front and back. After each defecation the anal region is to be thoroughly washed with soap and

ishing and illustrative experience that befell me during a brief sojourn as ship's [illegible] on re [illegible] of my [illegible]

scene of this delivery. Whereupon he promptly conducted me to the after part of the main deck, where, surrounded by a gleeful group of his fellow-countrymen, a large roundworm lay in the scuppers. And before I could quite realize the significance of the scene, he began obligingly to cough and retch—and in a moment, with the assistance of two fingers inserted into his throat, he had brought up another! But now for the illustrative part of the tale, so far as it concerns the drug under discussion. This man gave a history of malaria that had been "cured" two years before, and was certainly not suffering from any sort of febrile disturbance at the time of this incident; furthermore, at the examination of the crew six weeks previously, and often in deck encounters since, I had remarked him as an exceptionally robust and hearty fellow I therefore gave him 5 grains of santonin, 3 grains of calomel and a little sugar—with the result that within the hour he was in convulsions, from which he went into coma and only escaped foregathering with his Aztec fathers because they seemed not quite ready to call him in. Moral to adorn a dull tale: never give 5 grains of santonin to any man alive *if* it is desired that he continue in that condition.

Other Agents.—Carbon tetrachloride when given to ascaris-infested individuals may admittedly cause the worms to migrate or entwine themselves together and induce intestinal obstruction, and it has been alleged that gentian violet will do the same thing But Brown (1946) put the matter to the test with regard to gentian violet, and found that its administration for ten consecutive days did not produce findings suggestive of migration of the worm or of intestinal obstruction in twenty treated children; however, he did not find it very effective against ascaris either.

THE PIN-, THREAD- OR SEATWORM

Enterobius (Oxyuris) vermicularis is a frequent infester of the anal region in [illegible] It has been generally held that [illegible] (1944) says that in Amster- [illegible] fested. According to Oxenius (1944), the frequency of enterobiasis in Germany during War II added seriously to effects of the air raids in causing loss of sleep and consequent loss of productive capacity. Stoll (1947) estimates the over-all world figure at 209 million infestations. An intermediate host for this worm is unnecessary, the [illegible] The vicious circle [illegible] ch and develop in [illegible] pass down to the lower part of the large intestine, when the females are ready to deposit their eggs they crawl out of the anus and wander about the perineum, even entering the vagina at times; the crawling of the worms in the rectum and on the peri-

neum causes intense itching; in the process of scratching many of the females are crushed and their eggs liberated, the hands, contaminated with eggs, are ultimately carried to the mouth, and the whole circle is completed with the reinfestation which thus takes place. Recent studies have also shown that viable eggs contaminate the lower objects in rooms also, such as furniture legs, rugs, window ledges, etc.; Cram (1943) even found the eggs at all levels from floor to ceiling. Severe anal pruritus is the only definite symptom of pinworms, though it is perhaps not entirely incorrect to ascribe some of the nervous disturbances of young children, especially those with erotic manifestations, to this infestation. Jacobs (1942) felt, as the result of a study of a large number of infested children, that the following should lead one to suspect pinworm infestation: vaginal discharge, attacks of abdominal pain, anorexia, undernutrition, insomnia, nervousness, enuresis and pruritus ani; Cram (1943) agreed in the main except for the matter of the incidence of enuresis. Some observers believe that the worm is responsible, directly or indirectly, for many cases of appendicitis, but this is certainly not proved though the worms are many times found in that appendage when it is removed. Diagnosis is made upon finding the eggs in the feces by the salt flotation method, but the more frequently employed methods nowadays consist in applying an NIH swab to the perianal region (a glass rod to which is attached a small square of cellophane, this is stroked outward over the perianal mucosa and the cellophane square is then transferred to a glass slide and examined under the microscope), or the use of scotch cellulose tape applied to a wooden applicator in much the same way. A single NIH examination is from 40 to 50 per cent efficient; many observers have confirmed the finding of Sawitz *et al* (1939) that seven such swabbings, on alternate mornings, will detect practically 100 per cent of infestations. It is claimed by Schüffner and Swellengrebel (1943) that their pestle method is far more speedy and reliable than the swab methods.

THERAPY

The length of the life cycle of the pinworm, from the time the eggs are ingested to the time the females crawl out the anal opening, was formerly held to be a little more than two weeks. If, therefore, the conveyance of eggs from anus to mouth by contaminated fingers could be *absolutely* prevented for a period of two to three weeks, it was thought that the infestation would be cured. Now, however, with some investigators maintaining that the cycle may be several months in length and others that in some instances the eggs may be laid within the bowel and the cycle be completed there (the evidence for this latter contention is unimpressive), the hope of curing the patient with hygienic measures rigidly maintained during the period covered by one complete cycle is waning However, I shall continue to describe the methods, even though the feat is extremely difficult of accomplishment, nonetheless so because viable eggs are now known to survive quite a while on carpets, furniture, etc.

The treatment should begin with a full bath with soap and water, special attention being paid to the anal region. After this the anal region and the perineum are to be anointed with an ointment composed of 2 per cent of ammoniated mercury in equal parts of lanolin and petrolatum, a pad of cotton applied, and the child clothed in heavy drawers that are closed front and back. After each defecation the anal region is to be thoroughly washed with soap and

remains attached to the worms. (*b*) The following morning the patient should remain in bed without breakfast and should be given 10 minims (0.6 cc.) of *tetrachlorethylene* and 2 minims (0.12 cc.) of oil of chenopodium, which should have been thoroughly mixed and added to sugar in a teaspoon. (*c*) Two hours after administration of the anthelmintic there should be given a *follow-up* saline purge, and then following the bowel movement a light noon meal may be taken.

In the experience of Whittier *et al.* (1945), in Panama, the combination of hexylresorcinol by mouth (see Roundworm for dosage) and by enema (see Pinworm for dosage) was the most satisfactory of the several treatments they tried, though even it was far from productive of as good results as might be wished. They found both the fresh latex ("Leche de Higuerón") of the fig tree, *Ficus laurifolia*, and the proprietary preparation of same quite disappointing.

GUINEA OR MEDINA WORM

Dracunculus medinensis is a large worm that requires two hosts for the completion of its life cycle The free-swimming larvae penetrate and develop to a certain stage within the body of a very small crustacean of the genus *Cyclops*. When unboiled water containing this crustacean is swallowed man becomes infested. About a year after the ingestion of the larvae, the adult female worm works her way into the subcutaneous tissues in order to discharge her embryos outside the human body. Her presence is first manifested by the pruritus which is set up, then a cordlike lump can be felt beneath the skin; finally, there is a vesicle and then an ulcer, from an opening in the base of which the embryos are liberated in a milky fluid which exudes when cold water is brought into contact with the ulcerated surface. The infestation of the

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identical with *D. medinensis* in the fox, raccoon and

the United States and Canada, and that Chandler (1942) confirmed the finding in raccoons; all the human cases reported on this continent have been imported, however.

THERAPY

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certain to take place. The orthodox physician's most usual method of attack

is to inject 1:1000 solution of bichloride of mercury into the burrow, the attempt, which is usually unsuccessful, being made to remove the worm on the following day. One of my former students informed me several years ago that in Hong Kong the worms are caused to extrude in their entirety by keeping the ulcers covered with plain cold water dressings continuously for ten days to two weeks. Ransom states that Macfie had good results with the intravenous injection of tartar emetic, 1 grain being given every second day until a total of 6 grains had been given, but I do not know that anyone else has had this experience. Elliott (1942) described the successful emplo... thiazine in an elaborate injection techni... ty of this agent is sufficiently low ... to me that the method needs to be

TRICHINOSIS

Trichinosis is a disease that is acquired when the encysted larvae of *Trichinella spiralis* are ingested in raw or undercooked pork. The larvae are liberated by the action of the digestive juices, the adult worms quickly develop in the upper part of the intestinal tract, copulation takes place, the males die and the females burrow into the submucosal tissues whence they discharge the new crop of embryos into the lymph spaces. These embryonal forms are carried into the blood stream and conveyed to all parts of the body, some of the embryos also undoubtedly penetrate through the tissues by their own motile power. Ultimately they come to rest in the voluntary muscles, principally of the lower extremities, where the developing larvae give rise to an inflammatory reaction and are finally walled off by connective tissue, sometimes with calcification in addition. An individual cyst is barely perceptible to the naked eye. The hog becomes primarily infested from eating scraps of uncooked trichinous pork present in garbage, perhaps also very rarely from eating the carcass of a trichinous rat. Gould (1945) says that the average incidence of trichinosis among hogs in the United States during the past fifty years has remained practically unchanged at a level of approximately 1.5 per cent. According to Stoll (1947) *T. spiralis* is almost completely absent in man in the major portion of the world. East of Suez (more specifically Syria) all the way to San Francisco, as well as in Australia, in Africa and generally throughout the Torrid Zone, it is substantially non-existent as a human infestation; these are regions in which live about two-thirds of the earth's inhabitants. The classic zones of infestation have been in Central Europe and those parts of temperate America to which its emigrants with their pig-eating habits have gone. Gould (1945), pointing out that surveys of necropsy material in various localities in the United States have shown an average incidence of 16 to 36 per cent of trichinous infestation, feels as have others before him that the United States has the greatest problem of trichinosis of any country in the world; by an ingenious method of reckoning he estimated that each American during his lifetime consumes nearly 200 meals of trichinous pork. And at only one of these meals is it necessary for the pork to be undercooked or inadequately processed for infestation to take place. Meat packing plants under government inspection are required to produce processed products that may be expected to be free from viable trichinae, but non-processed pork prepared in such plants, and all pork prepared in plants not under government inspection,

ber of genera of both day- and night-biting mosquitoes, the larvae enter the body of the mosquito and undergo certain changes there, but it is important to note that since the adult worms cannot reproduce themselves in the human host the possibility does not exist for an individual to accumulate more filariae than were originally injected through the bite of the infected mosquito. The metamorphosed larva, being deposited upon the skin of another individual whom the mosquito bites at a later period, pierces the skin and enters the lymphatics, there to grow to adulthood, to copulate and to send showers of microfilariae into the lymph and the blood stream. It is felt that the acute symptoms of the disease, which rarely occur before an individual has been about three months' resident in a filaria infested region, are the result of irritative changes set up by the live adult filariae in lymphatic tissues and by allergic reactions to the dead adult filariae in the same location; plugging of the lymphatic channels causes a backing up of toxic products centrifugally, which would account for the so-called retrograde lymphangitis. Zuckerman and Hibbard (1945), in confirmation of Wartman (1944), found no histologic evidence of superimposed bacterial infection as a cause of lymphangitis in their series of cases. The microfilariae do not cause symptoms unless they may in some instances be responsible, as Neumann (1944) considered possible, for the giddiness that is a frequent complaint in endemic areas and rarely for the occurrence of retinal hemorrhages without other explanation. An acute attack ("mumu") consists of lymphangitis of an arm or leg, or more often of the scrotal region or the scrotal contents, accompanied by constitutional symptoms that in most instances are not very severe. The affected part is of course enlarged and erythematous and the lymphatics and regional glands are swollen and tender. The symptoms disappear completely in a few days, sometimes with subsequent intense itching and desquamation, but the patient is likely to [illegible] infested region it is [illegible] ntirely [illegible] g-time resident of an infested area attacks cease to recur but the chronic [illegible] rming [illegible] The establishment of elephan- [illegible] and thus to cause the [illegible] Next in frequency to the legs, the scrotum is involved; elephantiasis of the arms, the penis, the scalp, the breasts and the subcutaneous tissues have also been reported. In some geographical regions chyluria is usually a symptom of the disease in [illegible] duct and the bursting [illegible] gs in the groin are fre- [illegible] mon. Leg abscesses in [illegible] during War II many thousands of our personnel contracted filariasis. According to Coggeshall [illegible] cases were diagnosed in the Marine Corps and the United [illegible] Army [illegible] ring [illegible] cro- [illegible] only [illegible] hese negative findings for the reason that, according to [illegible] has forms are usually not found before the seventh year after infection has occurred. Dickson *et al.* (1943), studying this matter in a highly endemic area,

found microfilariae in only 1 6 per cent of 244 children under five years of age. A negative finding does not of course mean that the individual does not have the disease but only that sufficient time has not yet elapsed for the number of microfilariae to have risen sufficiently high for their easy detection to occur,

tissue reaction around the adult worm hinders access of the microfilariae to

an absence of microfilariae (b) The diagnosis of an early case rests principally on the clinical findings because neither the complement fixation test nor the several intradermal tests have as yet proved entirely satisfactory. (c) A non-native resident of an endemic area is well advised to leave the region if possible after he has had an attack because the likelihood of ultimate elephantoid deformity increases with an increasing number of attacks, though from Webster's (1946) study of white persons of missionary and other categories

lightness of the infestations, but also that repeated biopsy examinations have

the non-filarial causes for elephantiasis, scarring, metastatic cancer, thrombophlebitic disorders, hemangiomas, lymphangiomas, Milroy's disease and lipodystrophy. (e) The major psychoneurotic problem posed by men who have contracted filariasis, and who have seen in native populations the dire results of continuous reinfection over the years, has been stressed by numerous

opinion has more recently been expressed by many others. The reasons for

recent years but have not given rise to fresh cases of filariasis in this country, though many of these individuals had come here because they had experienced early infection in their own native region; a focus of infection existed for a good many years in Charleston, South Carolina, but it never rose above a smouldering stage and has now died out; (there was also a period during which filariasis was commonly diagnosed in Australia, having arrived with infected laborers from the Central Pacific Islands, but there too it disappeared spontaneously); a few infestations presumably acquired in regions in the United States other than Charleston have been reported but the number is much less than a dozen and they do not fit into any present epidemiologic picture. (g) The studies reviewed by Hawking (1943) proved that microfilariae introduced by blood transfusion can live in the blood of a nonimmune subject for as long as eight days; however, the disease filariasis cannot be so transmitted since its etiologic agent is the larval form of the filaria after it has undergone certain changes in the body of its insect vector. However, since the maximum incubation period in filariasis is unknown but is probably a period of years, a civilian physician should recognize that symptoms and signs of filariasis may appear for the first time in returned soldiers long after they have left regions in which the disease is endemic.

Filariasis due to *W. bancrofti* and *W. malayi* occurs in the tropical belt all around the world, but the distribution of endemic centers within this belt is a very unequal one; it is not possible to mention, in a work so limited as the present one, all the places where this disease has been diagnosed. Stoll (1947) estimates that the number of people infested is probably about one-third the population of the globe, or 758 million people, and that even if one reduces this figure as much as possible to take into account local conditions as applying to the vector, one comes out with a world total of 189 million cases. The disease is especially prevalent in Africa and in the Samoan area of the Pacific.

Loa loa is a filarial worm that spends its larval stage in the blood, with the diurnal periodicity of *W. malayi*, but wanders about in the subcutaneous tissues during its adult life. The name "Calabar swelling" has been applied to the fleeting edemas caused during the course of these wanderings; areas of localization in the spleen may also react with inflammation and fibrosis. The parasite sometimes crosses the eye, giving rise to conjunctivitis during its passage. A fly of the genus *Chrysops* is the vector of this form of filariasis. Loiasis is confined to a very small area on the West Central coast of Africa, where Stoll (1947) says there may be as many as 13 million cases. The disease [illegible] I saw such [illegible]

[illegible] the service in Africa during War II.

Onchocerciasis occurs in Guatemala and certain southern provinces of Mexico as a filarial disease characterized by the presence of subcutaneous fibromatous nodules on the head and in many cases disturbances of the eyes and loss of vision. The tumors contain adult male and female *Onchocerca volvulus (caecutiens)* and not mosquitoes but three species of *Simulium* flies are the insect vectors. Dampf (1942) felt that onchocerciasis will certainly spread along the Pan-American Highway unless certain definite precautions are taken. In some portions of tropical Africa essentially the same disease prevails, but there the nodules occur on the body more often than on the head. It is also felt by some observers that in Africa there is also a reservoir of the

disease in cattle and certain of the larger wild animals, notably antelopes. Stoll (1947) says that the total number of cases of onchocerciasis in the world does not exceed 20 million

THERAPY

The symptomatic treatment of early filariasis involves no especial difficulty as the attacks are of short duration though often very distressing in nature.

[illegible]

may at times be controlled by elevation of the pelvis and reduction of the fat in the diet, but Mohadevan (1941), in a symposium on filariasis in India, expressed the opinion that fat should not be excluded from the diet of a chyluric patient for the reason that he is already losing much of what he should have retained.

In Puerto Rico, Culbertson *et al.* (1946) employed neostibosan with apparently excellent results in the treatment of thirty-five patients; all of them were asymptomatic except one who had chyluria and another who had periodic lymphangitis, but all had microfilariae in the peripheral blood Of the several dosage schemes employed the most intensive consisted in two or three intravenous injections of the drug per day, the dose rapidly being increased from an initial injection of 100 mg to 500 mg by the fourth or fifth dose and being continued thereafter at the rate of two or three 500 mg. doses daily until a total treatment period of fourteen days had been run. It seems that twenty of the thirty-five patients were apparently entirely cured of the infection as shown by their loss of all microfilariae during a period of observation of five to fifteen months; ten others lost more than 80 per cent of their circulating microfilariae and appeared likely to lose the remainder within a few additional months Fifteen control untreated patients were all still infected after observation from fourteen to seventeen months. The immediate reactions of patients to neostibosan were slight, consisting chiefly of nausea and vomiting, usually patients acquired tolerance for the drug within a few days and in no case was it necessary to stop its administration because of toxicity, nor did it give rise to elephantiasis in any of the cases.

Brown (1944) used anthiomaline (lithium antimony thiomalate) on twelve filariasis patients in the Virgin Islands who had microfilariae in their blood.

[illegible]

respond at all to the treatment. Brown (1945) has expressed the opinion that neostibosan has the advantage over anthiomaline of being less toxic.

I think it important to point out with regard to the use of these antimony compounds in filariasis that such measures cannot be expected to be of any value in the treatment of the acute stage of the disease as it was experienced by our troops during War II, and furthermore that the mere killing of microfilariae in individuals constantly exposed to reinfection is not likely to be of much value. Of course if it can be fully demonstrated that the effect upon the microfilariae is a reflection of the induced death of the adult worms perhaps something more will have been accomplished. The studies of Welch *et al.* (1947) with the cyanine dyes will be watched with much interest

Burhans *et al.* (1944) said that they had tried x-ray therapy in Navy personnel and found it to cause prompt decrease in the size of enlarged lymph glands, but Coggeshall's (1946) subsequent statement was not confirmatory.

The treatment of elephantiasis is principally surgical; scrotal cases give the most satisfactory results, but the operative procedures so far evolved apparently still leave much to be desired. Bowesman (1938) reported that *the condition is simply and safely alleviated to some extent by weekly injections* into the femoral artery of 2 to 3 cc of sterile 10 per cent glycerin. Knott (1938) said that prolonged firm bandaging induces prompt symptomatic relief and effects gradual removal of the lymphedema.

In loiasis the parasite may be removed by simple incision when it crosses the eye; its removal from the subcutaneous tissues is sometimes accomplished in the same manner.

In onchocerciasis, the tumors (and the contained adult parasites) can be easily removed under a local anesthetic, but in some cases the microfilariae continue to circulate in the body for at least several years Chemotherapeutic agents *have failed in both this disease and loiasis.*

STRONGYLOIDES INFESTATION

Physicians in the southern United States are becoming very familiar with this entity that has long been recognized in other subtropical as well as tropical regions. Among admissions to a New Zealand hospital *from the* Solomon Islands during War II, Liebow and Hannum (1946) reported an incidence of strongyloides infection in 7.4 per cent of 633 stool examinations, placing *this infection next in frequency to ancylostomiasis* Stoll (1947) feels that estimates of the world-wide incidence of the infection are at present inadequate but that a tentative figure is 35 million. The life cycle of the causative worm, *Strongyloides stercoralis*, is much like that of its close relative, the hookworm, except that it embeds in the mucosa instead of *lying* free out in the lumen of the intestine, and that during the time in which the larvae are migrating from the capillaries into the bronchioles an acute inflammatory reaction may take place in the lungs; furthermore autoinfection can occur since the larvae are capable of penetrating the intestinal mucosa and the perianal skin to continue the cycle without going through a period *of further development* on the ground. In very light infestations there may be no symptoms, but in moderately heavily infested individuals there is diarrhea with distress after meals, alternating at times with constipation, in some cases there is intractable diarrhea, great emaciation and, occasionally, severe toxic edema. Positive diagnosis can be made only on finding the typical

motile larvae in the stools, since the eggs closely resemble those of the hookworm. Whitehill and Miller (1944) reported a case and cited another from the literature in which the larvae of *S. stercoralis* were present in the urine.

THERAPY

The anthelmintic drugs have failed here since the worms are embedded in the mucosa and cannot be reached by an agent that is not absorbed.

Gentian violet has been used with fair success off and on since its introduction into this therapy by the Dutch in Java a number of years ago. Two enteric-coated 1/2 grain (30 mg) tablets of the medicinal dye are given adults three times daily before meals for sixteen days. The treatment is said to kill the adult worms but not the larvae or the eggs Shikhobalova and Semenova (1942) found larvae reappearing one or two months after a course of treatment had ceased in some of their small series of cases Faust (1939) said that in refractory cases 25 cc of a 1 per cent solution of medicinal gentian violet can be introduced by transduodenal intubation, leaving the tube in for an hour after the introduction of the drug and then carefully withdrawing it Willard (1946) reported three patients who responded well to the oral administration of gentian violet; his other four patients responded to the intraduodenal instillation of the drug though in two of these patients repeated small doses had to be given because of immediate nausea and vomiting with larger amounts. Simpson (1939) reported that he sometimes succeeded with the use of iodine. a saline is given in the evening, and the next morning, withholding breakfast, a duodenal tube is passed and the stomach is irrigated and the duodenal contents aspirated; then 4 cc of compound solution of iodine (Lugol's solution) are introduced and the tube removed, the treatment being repeated on alternate days until the duodenal contents and stool are negative for ova, parasites and larvae.

HOOKWORM DISEASE

(*Uncinariasis, Ancylostomiasis*)

Hookworm disease is caused by two species of intestinal worms, *Ancylostoma duodenale* and *Necator americanus*. The life cycle of these worms is very simple, since man is the only host The eggs are passed in the feces of an infected person; if the stool is deposited on the soil under suitable condi-

lungs where the alveolar walls are pierced and the free air spaces entered; in the next stage the larvae pass up the trachea and larynx and then down through the esophagus and stomach into the middle portion of the small intestine, where they attach themselves and attain maturity. From six weeks to two months after the larvae have penetrated through the skin the adult female worms are laying eggs that are passed out with the feces. Individual worms live as long as seven to ten years, during which time they disengage and reengage at many sites in the intestinal mucosa. The worm passes much blood through its body and each time the head is withdrawn a point is left

which bleeds for some time, as the head of the worm secretes an anticoagulant substance. It has been felt in the past that these worms *secrete a hemolytic* toxin, but as the point has never been proved the consensus is now that the anemia of hookworm infestation is due entirely to gross loss of blood as described above Bonne (1942) alleged that occasionally in *A. duodenale* but not in *N. americanus* infestation the worm may invade the submucosa of the intestine and give rise to inflammatory reactions there.

Stoll (1947) places the total number of cases of hookworm disease in the world at 457 million. It prevails throughout the tropics and also in many warm, but distinctly subtropical, regions where it is principally a disease of "native" populations. Endemic foci also exist in the Witwatersrand gold mines in the Transvaal and in the the coal mines of such of the cooler portions of the globe as central Europe and the south of England. Miners contract the disease by contact of their hands, arms, knees, elbows, or buttocks with feces-contaminated soil in the mines, but everywhere else it is almost exclusively contracted by those who go about barefooted in regions where the first principles of decency in the matter of personal and communal hygiene do not obtain.

record. Hookworm problems still exist over large areas in our

Commission (1910–1914). Actually in rare instances the disease may be contracted in endemic areas by persons whose personal habits would seem to exclude the possibility, the infestation occurring in these cases *via* the mouth. In this connection it is interesting to note that Loughlin and Stoll (1947) have shown that wearing apparel and bed-clothes when contaminated with infested fecal matter and allowed to remain damp and unwashed for some days will harbor appreciable numbers of hookworm larvae.

The classical infestation of natives begins as soon as they are old enough to range very far away from the house door and continues *as long as* they go about barefooted in the endemic region. The passage of the larvae through the skin causes in most cases a local vesicopustular lesion known as "ground-itch." After a variable period of time, depending upon the degree of the infestation

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heavier than in the temperate zones and the nutrition often very poor, death primarily due to hookworm disease is not rare, the terminal picture is said to be one of extreme anemia and physical exhaustion, a nephrotic syndrome with

is no manifest anemia; in the second type the production is unable to counterbalance the loss and a hypochromic anemia results; and in the third type the bone marrow is exhausted and a severe irreversible aplastic anemia develops.

Most *et al.* (1946) performed routine stool surveys of men returning to our country from various Pacific islands after War II and found an incidence of hookworm infestation 1 8 times that of troops who had served only in this country. But Levine (1946) concluded from his experience in the Southwest Pacific area that significant anemia from hookworm did not develop in American troops subsisting on the regular Army diet and that indeed from both the

reinfestation, the primary infestation with hookworm dies out in from a few months to several years.

It is thought the mysterious AAA disease of the Ebers papyrus, dating from the Eygpt of about 1550 B.C., might have been hookworm; other intestinal worms are with certainty mentioned and prescribed for in that ancient compilation. As century followed century, from being known as Egyptian disease it came to be called tropical chlorosis, miner's anemia and St. Gotthard tunnel disease. In 1843, Dubini described *A. duodenale*, and in 1866 Griesinger showed its causal relation to the disease *N. americanus* was discovered by Stiles in 1902. In 1898 Looss discovered the remarkable route by which the larvae reach the intestine

THERAPY

Extensive experience in the campaigns for control of this malady has conclusively shown that routine drugging of individuals who must remain in endemic regions is of secondary importance to the sanitary measures necessary to prevent reinfestation. Still today, however, both within and without such regions, chemical disinfestation must often be resorted to. The following are the chief of the anthelmintic agents employed. Their toxicology is presented at the end of this chapter.

Tetrachlorethylene.—The superiority of this drug seems to be well estab-

treatments with tetrachlorethylene are about equivalent to and much safer than a single dose of carbon tetrachloride in dislodging hookworms. It is prob-

ably advisable to clean out the intestinal tract by a magnesium sulfate purgative the evening before (though this may be omitted), the treatment being given next morning, omitting breakfast. The average adult dose is 3 to 4 cc divided into six capsules, or the liquid may be poured onto sugar. Immediately after taking the drug a magnesium sulfate purge is taken. Or the drug may

reexamination after two weeks, the treatment may be repeated. The dosage for children is 0.2 cc. for each year of age up to fifteen. The drug has a more pronounced taste than carbon tetrachloride, but as pointed out by Hare and Dutta (1939) it is pleasant to smell, does not burn the mouth and produces a slight drowsiness enjoyed by coolie populations; Lambert (1933) had earlier

ature.

e (see

below) for it increases the toxicity of both.

Carbon Tetrachloride.—This drug is tasteless and very effective. In Egypt Tomb and Helmy (1933) had only 19 deaths among 1,600,000 treated patients, and they said that most of these could have been prevented. Carbon tetrachloride is given in the same dose and by the same methods as tetrachlorethylene (see above). Pregnancy is not a contraindication to the use of the drug, *which is probably true of tetrachlorethylene also, though the fact has not* been definitely established so far as I am aware.

Oil of Chenopodium.—This drug is given mixed with a dose of castor oil appropriate to the patient's age, which seems definitely to lessen absorption and hence toxicity Mukerji and Ghosh (1943) found that oil of chenopodium deteriorates markedly upon standing whether kept in the dark or in the light. Dosage is 1.5 to 2 cc. for the adult, and 0 05 cc. for each year of age up to twenty for children.

Oil of chenopodium is also quite effective against roundworm, a matter of some importance, as indicated below It has been given in millions of cases with only a few recorded deaths (Smillie said, in 1939, that he had had 22 deaths in over a million persons treated in Brazil) and even the number of instances of mild or moderately severe reactions is very small; nevertheless, it

...llorethylene or carbon tetra-

n combination with tetrachlorethylene when *there* is a mixed with round- and hookworms The usual procedure under these circumstances is to give in one dose a mixture of 0 05 cc. of oil of chenopodium for each year of age up to twenty years and 0 1 cc of tetrachlorethylene for each year of age, the adult dose being 1 cc. of oil of chenopodium *plus* 2 cc. of the other drug One must be sure to follow this mixture with salts and not castor oil for the latter increases the toxicity of tetrachlorethylene Andrews (1942), preferring *less potent agents, stated* that when both roundworms and hookworms are present hexylresorcinol followed by tetrachlor-

ethylene or several hexylresorcinol treatments in rapid succession will give most satisfactory results Miller *et al.* (1945), in the Canal Zone, used these two drugs in succession with satisfaction. For methods of giving hexylresorcinol see Roundworm.

Iron Therapy.—There is only so much iron in the body and most of it is in [illegible] If the hookworm infestation has been overwhelm-

Rhoades *et al.* (1934), showed that following anthelmintic treatment alone it required one to two years for hemoglobin values to reach a satisfactory level but that the supplementary use of iron much improved the picture—facts which have been empirically known for a long time of course in all lands with heavy hookworm infestation.

CREEPING ERUPTION

Creeping eruption is an acute inflammatory condition of the skin due to the larva of the cat or dog hookworm, *Ancylostoma braziliense* This malady is quite prevalent in warm countries, the cases in the United States being seen principally in the South Atlantic coastal area although the disease occurs also at a considerable distance inland According to Hailey (1940), creeping eruption begins as an inflammatory papule that persists from a few hours to several days From this papule a blunt pointed elevated line of protrusion extends itself to mark the progress of the nematodal invader, the lesion advancing at the rate of one-quarter to one or more inches within twenty-four hours The parasite frequently follows a tortuous course, going about in circles and turning back upon its previous course Vesicles, bullae, hemorrhage, pyogenic infection, edema and local urticaria are common primary and secondary lesions accompanying creeping eruption and greatly altering the size and appearance of the lesions Infection is acquired through contact with the infected soil

In twenty-six of the fifty-two cases of creeping eruption studied by Wright and Gold (1946) for a period of fourteen days or longer, there developed transitory migratory pulmonary infiltration and peripheral eosinophilia with almost complete absence of clinical signs or symptoms of systemic disease; it was felt that in these cases the lung reacted as a shock organ to the blood-borne antigens from the larvae and the cutaneous lesions and that therefore infestation with *A. braziliense* might be added as a hitherto unreported etiologic factor in the production of Loeffler's syndrome

THERAPY

The organic antimonial compounds, fuadin and neostibosan, have been used with some success in these cases (see Index for methods) Hitch (1946) has also reported the successful employment of mapharsen None of these agents is entirely satisfactory, however, since they do not seem to effect cure

in all cases and admittedly they are quite potent agents to be used in a relatively benign condition such as creeping eruption. Sometimes the lesions are satisfactorily treated by freezing them with the ethyl chloride spray. Hailey (1946) has used with some satisfaction a poultice made of fresh onions: large white onions are grated coarsely and spread over gauze previously spread with petrolatum to hold the onion in contact with the skin that has been thoroughly cleansed with soap and water before the poultice is applied. The poultice is covered with wax paper or some impervious material and left on all night. In Hailey's experience three to seven nightly poultices cured the four patients in whom he tried this treatment.

THE TOXICOLOGY OF VERMIFUGES

Aspidium.—The milder symptoms consist in colic, diarrhea, headache, dizziness, dyspnea and yellow vision. Any one or all of these symptoms are not infrequently seen in slight degree, but more serious manifestations of poisoning, such as violent muscle cramps, jaundice, evidences of renal injury, blindness, delirium, convulsions and coma are very unusual; death is rare.

The stomach should be emptied by the use of a nondepressing emetic, such as powdered mustard (a teaspoonful in a cup of lukewarm water), copper sulfate (4 grains, or 0.25 gm., in water), or zinc sulfate (15 to 30 grains, or 1 to 2 gm., in water). A full dose of magnesium sulfate, 1 to 1½ ounces (32 to 48 gm.), should be given to flush out the bowel. The patient may be stimulated by heat, strychnine, caffeine, digitalis, etc., as indicated by the symptoms. Recovery is slow.

Pepo.—The toxicology is unimportant.

Pomegranate.—The toxicology is unimportant.

Pelletierine Tannate.—Mild toxic symptoms, which are frequent, consist in dimness of vision, dizziness, muscle cramps, formication, weakness and trembling. Overdoses cause partial blindness with dilated pupils in addition to the above symptoms in aggravated form; there is also violent headache, vomiting and diarrhea, sometimes convulsions.

The treatment is the same as for poisoning with aspidium, but when an overdose of pelletierine has been taken one should proceed very cautiously as these patients are profoundly prostrated.

Santonin.—Overdoses of this drug may cause early vomiting, abdominal cramps and sometimes, but not always, diarrhea. The patient is dizzy and very weak and may complain of headache and painful urination; it is said that hematuria may also occur. In severe cases there is an astonishing fall in temperature and the patient may go into violent convulsions; coma usually precedes death.

The treatment is the same as for poisoning with pelletierine. Every attempt must be made to keep the patient warm, and all available stimulants may be tried. An anesthetic, carried only to a light stage of relaxation, will control the convulsions, but if the patient sinks into coma he is almost certain to die.

Yellow vision often occurs in the routine use of the drug but is of no importance if unaccompanied by other symptoms.

Oil of Chenopodium.—The symptoms of chenopodium poisoning are referable to the central nervous system and consist in nausea and vomiting, diz-

ziness, internal ear deafness, tingling of the hands and feet, muscular incoordination and semicoma. The kidneys are also affected as is shown by albumi-

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into gastro-intestinal tract, severe jaundice after forty-eight hours, urine scanty and highly bile-stained

Roundworm.—The drug may so greatly stimulate ascarids that writhing masses of these worms can be seen through the abdominal wall. Pharyngeal

lack. Since such lack is rarely seen except in poorly nourished individuals, all such patients should have their weight improved and the calcium supply restored before using carbon tetrachloride in them.

lavaging might be advantageous since carbon tetrachloride is very soluble in oil) (b) Force fluids by mouth and intravenously (c) Administer hypertonic dextrose solution intravenously two to four times daily and 10 to 15 cc. of 10 per cent calcium gluconate solution by the same route every five or six hours for the first two days, then two to four times daily depending on severity. (d) Give a high carbohydrate, low fat and low protein diet and 20 grains of calcium

An interesting therapeutic approach in cases of acute poisoning was made by Beattie *et al* (1944), who based their treatment upon the belief that the intimate cause of liver disturbance induced by carbon tetrachloride is an abnormal metabolism of methionine and related compounds. To a patient who had swallowed accidentally 30 to 40 cc. of carbon tetrachloride they gave 2 gm of *dl*-methionine by mouth, three hours later 1 cc of a casein-digest-methionine solution by vein, after a short time 5 cc. more of this solution, and then finally continuous infusion of the same by drip apparatus at the rate of about 2 cc per minute. The infusion was stopped after three hours when 436 cc. had been introduced and the next day the liver was no longer tender and the edge had much receded. On the next day, however, it enlarged again

and the patient was given 2 gm. of methionine by mouth in the morning and another 2 gm. in the evening; on the next day the liver had again retracted, no more amino acid therapy was given and the patient recovered.

Tetrachlorethylene.—No serious toxic symptoms have been reported, except for two instances recorded by Sandground (1941) in which the patients were said to have gone into coma lasting several hours. A few patients complain of *transient dizziness and giddiness, and mild gastro-intestinal symptoms* are sometimes experienced.

Hexylresorcinol.—No systemic reactions of a serious nature have been recorded.

Gentian Violet.—The symptoms induced by this drug are principally gastro-intestinal and, as recorded under Pinworm, quickly subside, contraindications are given in the same article. I have seen no report of serious systemic poisoning from this drug used as an anthelmintic.

ALLERGIC DISTURBANCES

HAY FEVER

ever, that unusual weather conditions can affect pollen production very significantly. The pollens of the common trees, grasses and ragweeds are the most usual offenders, conferring, respectively, the titles "spring," "summer" and "fall" hay fever. The symptoms are itching and congestion of the eyes, violent paroxysms of sneezing and a thin irritating discharge from the nose, often

days though very many sufferers are more or less incapacitated for active participation in affairs throughout the entire "season." Some of the patients experience asthmatic attacks in conjunction with their hay fever. Those who

between seasonal and perennial hay fever can be by no means always sharply

and not infrequently leads to violent asthmatic death. Animal danders, vegetable powders, house dust, foods and drugs are held to be principally responsible for vasomotor rhinitis.

I believe that the earliest clear account of this disease was that of John Bostock, in London, in 1819. Abundant experience in War II supported the observations of Clearkin (1943) and Cook and Kawasaki (1943) that hay fever had earlier been considered to be absent from the tropics and subtropics apparently only because it had not been looked for. The American Indian and the Negro are thought to be much less susceptible to the disease than the members of other races, at least in the western hemisphere.

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mucous membranes, however, nowadays there is good reason to believe that a third factor is often of *great importance*, and that in states of status asthmaticus *it may be by far the most important* factor, namely, the actual blocking of the bronchi with accumulations of a very tough and tenacious mucous. *But the fundamental* cause of the condition remains unknown, though many of the cases rest upon an allergic basis. The attacks may last *for a few minutes* to several hours and are very distressing, though death from asthma *per se is unusual in the purely extrinsic type of the disease* (see below for classification of types). Characteristically, the patient coughs at the end of each attack and raises sputum containing Charcot-Leyden crystals and the bodies known as Curschmann's spirals These attacks may be infrequent or they may occur every day or several times during the night over a long period. *Osgood (1943) finds that the degree of systolic blood pressure* fluctuations occurring synchronously with the respiration offers an approximate indication of the degree of respiratory obstruction present, Rackemann (1944) finds these fluctuations occurring more frequently in older persons who have emphysema. In simple uncomplicated asthma relaxation is usually complete between spasms, but most long-standing cases are complicated by emphysema and chronic bronchitis and are therefore "wheezy" and somewhat distressed at all times. Unless complicated by the two diseases just mentioned, pain in the chest and cyanosis are rare during attacks. Just as we had settled down comfortably in the belief that "cardiac asthma" is always a state characterized by the mere coincidental occurrence of asthma and cardiovascular disease, Craige (1941) analyzed seven asthmatic deaths and found it not unreasonable to conclude that, at least in severe status asthmaticus, signs of right ventricular failure may sometimes appear and be due entirely to extracardiac factors; the findings of Schiller *et al.* (1943) were confirmatory. Schwartz (1945) has collected from the literature twenty-five case reports, to which he added one of his own, of spontaneous mediastinal and subcutaneous emphysema complicating bronchial asthma, spontaneous pneumothorax is a very rare complication. A number of observers have stated that there is a tendency toward hypoglycemia in asthma, and Abrahamson (1941) pointed out that the concept of hyperinsulinism underlying asthma offers an explanation for the frequency of nocturnal attacks; but upon the other hand, Goltman (1942) felt that diabetes may be associated with asthma much more frequently than has been suspected. Tocker and Davidson (1944) found that asthma improves during the period of activity of a tuberculous process.

Cases of asthma denominated "extrinsic" are believed to be caused by hypersensitiveness to some foreign substance outside the body, the sufferer [illegible]

comprises cases believed to be due to infection in the upper or lower respiratory tract, cases reflexly caused by bad teeth, nose and throat pathology, constipation, cholecystitis, or other well-defined foci of infection, and cases more or less directly associated with such conditions as pregnancy, obesity, nervousness and bad hygiene (the latter to include such items as an unwise dietary schedule, a lack of proper fresh air and exercise, insufficient intake of fluids and continued overwork without proper rest periods) The "miscellaneous unclassified" cases are, of course, just what the name implies.

Flensborg (1945), investigating the fate of children in whom asthma was diagnosed when they were very young (in the majority of cases before the age of five years), found that in about 40 per cent of the 298 patients the attacks had ceased, most of them ceasing in boys between twelve and fifteen years of age and in girls between nine and twelve years of age. The great majority of patients who continued to suffer from asthma at the time of the inquiry felt well in the intervals between the attacks, although about 47 per cent of them experienced dyspnea upon exertion and about 41 per cent suffered from chronic cough. In about 46 per cent of the total group of patients the asthma had seriously interfered with schooling and about a third of those who continued to experience asthma after the fifteenth year had found that the disease considerably interfered with their choice of a vocation. It would seem that the asthmatic who develops the disease after the age of forty, particularly if it is of the intrinsic type, is the individual most likely to die therefrom. Rackemann (1940) reported a mortality of 8 per cent in 283 patients with intrinsic allergy, periarteritis nodosa sometimes occurs as a complication in these cases. Gaarde *et al* (1942) found that about 14 per cent of a consecutive series of 169 cases of asthma, nearly equally distributed between the two types, developed significant pulmonary complications when the patients were subjected to major surgical procedures. Rackemann (1945) called attention to the general debility sometimes manifested by asthmatic patients.

It is commonly held that asthma is a rare disease in American Indians, but Derbes and Engelhardt (1943) found it certainly not an uncommon disease in the Negro. Cook and Kawasaki (1943) frequently encountered asthma as a quite severe disease in the semitropical Hawaiian area, and Leopold (1945), Winkenwerder (194[illegible] and since War II have found that [illegible] humidity with frequent rain can b[illegible] continuation of chronic perennial bronchial asthma. In an article on the health of the inhabitants of the remote island Tristan da Cunha, Woolley (1946) said there is no doubt of the hereditary nature of asthma among these isolated people whose complete pedigrees are known for seven generations.

ANGIONEUROTIC EDEMA AND URTICARIA

Urticaria, or "hives," is characterized by the sudden appearance in the skin of a firm, elevated, whitish patch surrounded by a pink zone and accompanied by intense itching or stinging sensations. The lesion may be single or multiple and usually resembles in size the wheal caused by the ordinary mosquito bite, in the cases known as "giant" urticaria, however, the individual lesions are much larger than this and several often coalesce to form a relatively enormous patch, while in infants and young children urticaria frequently assumes a papular, vesicular, or bullous form. The wheals disappear in a few minutes to hours or, in the more severe cases, may persist for several days or even weeks. It is usual for hives to appear in crops with relatively long asymptomatic periods between, but some individuals are rarely free from these distressing lesions for more than a few days in succession. In angioneurotic edema the subcutaneous tissues as well as the skin participate in the transient swelling that usually affects the forehead, eyelids, or lips and is only rarely accompanied by pronounced subjective symp-

toms; when the internal organs are involved also, as is very occasionally the case, the symptoms may of course simulate almost anything. All the recorded fatalities have been due to sudden edema of the larynx.

FOOD ALLERGY

It is not possible in a single small volume of this nature to describe the host of ailments that investigators nowadays recognize as being in all probability allergic manifestations to specific food substances; chief among them, however, are many cases of the following: migraine, hay fever, asthma, eczema, several other dermatoses, gastro-intestinal disturbances simulating any of the well-known acute or chronic syndromes, some cases of urticaria and angioneurotic edema, and, one may add, many other ailments whose allergic nature is oftentimes not suspected until demonstrated through proved hypersensitivity to a food substance. A peculiarity of food allergy is that after a time it usually involutes spontaneously and is replaced by an inhalant type of sensitivity; Chobot (1947) says that 98 per cent of food-sensitive children spontaneously lose their sensitivity by the time they are five or six years old and that this is the explanation for the infrequency of occurrence of food allergy in the adult asthmatic patient. Just why an adult will suddenly develop intolerance for a food that he has eaten with impunity all his life is as yet an unsolved puzzle, but I believe there is currently much acceptance of the concept of temporary alterations in the permeability of the gastro-intestinal tract for certain proteins. Squier (1940) made the point very positively that a gastro-intestinal examination by a competent roentgenologist, to rule out as nearly as possible organic disease, is an indispensable first step if one is dealing with suspected gastro-intestinal allergy.

SERUM DISEASE

Serum disease is an allergic reaction caused by the parenteral introduction, by whatever route, of foreign serum. The usual symptoms are a mixture of urticaria and erythema, fever, arthritis without pronounced objective changes in the joints, swollen and tender lymph nodes, and edema of various portions of the body accompanied by urinary evidences of temporarily impaired renal [illegible] internal organs may give rise to [illegible] m disease is not kept [illegible] wing the introduction of tetanus antitoxin, severe neuritis occurs. The time elapsing between the giving of the serum and the appearance of serum disease *is usually* seven to twelve days; in most cases the symptoms disappear in four to six days, but occasionally they persist for as long as two weeks. Recovery is the rule, though relapses are not uncommon. Kojis' (1942) exhaustive review of this subject is commended to the reader.

PHYSICAL ALLERGY

The demonstrations of Duke, confirmed by others, have impressed the profession with the fact that any of the bizarre manifestations commonly laid at the door of neurasthenia, psychasthenia, vagotonia and so on, as well as the more orthodox allergic syndromes, may not infrequently be due to heat, effort, cold, or light sensitiveness.

DRUG ALLERGY

In recent years evidence has been accumulating that sensitization to ordinary as well as to some extraordinary drugs is a much more common occurrence than had been previously suspected I cannot gather together here, merely to

LOEFFLER'S SYNDROME

mucoid sputum occasionally containing a few eosinophils Physical examination only occasionally revealed a few scattered rales and a fine friction rub. In about a third of Loeffler's fifty-one cases the disease had been discovered by routine roentgenograms and its presence had not been suspected before, the

ety of antigens, and hence that it was an allergic manifestation Since Loeffler's reports numerous other cases have been recorded and a number of reviews of

THERAPY OF THE ALLERGIC DISTURBANCES

The Antihistamine Agents.—In recent years it has become profitable to

quantities to be significant in the event that it were released into the blood

stream; (c) the anaphylactic reaction in the dog is accompanied by the prompt appearance in the blood and th

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histamine from the tissues into the blood stream and that it is this released histamine that sets off the train of allergic symptoms; (e) the attempt to develop agents designed to bl

recommended an oral dose for young children of 2 mg. per pound, the total to be divided into two to four doses. The contents of the capsule, or a crushed tablet, may be mixed with syrup or jelly. The average dose orally for older children and adults is 50 mg. three or four times daily, but in the use of these drugs it seems advisable to give the first dose a full chance to act before deciding upon the intervals of administration for sometimes considerable symptomatic relief follows the taking of a single dose. It has been suggested that benadryl may be given intravenously or intramuscularly in solutions of 10 to 20 mg. per cc , but McElin and Horton (1945) found that when given intramuscularly the drug causes pain with erythema, induration and tenderness; parenteral administration of pyribenzamine is not recommended Friedlaender and Feinberg (1946) found that even a 0 5 per cent solution of benadryl is too irritating for local use in th

very cautious in adopting such a procedure in asthma. In the main, the maximum response to these agents occurs in twenty to sixty minutes after oral administration and generally lasts for several hours Neoantergan has of course not been used as much in this country as either benadryl or pyribenzamine; Hunter (1947) feels that initial dosage by mouth should be 100 mg. three times daily, increasing as required to a maximum of 1.0 gram a day, and that the drug should not be used parenterally.

Effectiveness in Hay F

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indicated in 59 to 75 per

Bowen' (1946) declared that 84 per cent

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rather sobering note was introduced by Friedlaender (1946), who was able to attribute improvement definitely to benadryl in but a small percentage of his cases if he took daily pollen counts and prevailing atmospheric conditions into account and employed control groups. Feinberg (1946) obtained benefit from neoantergan in 65 per cent of his sixty cases.

Effectiveness in Vasomotor Rhinitis.—I think it will suffice to say that there is lack of agreement regarding the amount of relief obtained with the use of these new drugs in vasomotor rhinitis; this was reflected in the symposium of the American Academy of Allergy, above referred to, in which reports varied from 28 to 85 per cent of effectiveness. Perhaps pyribenzamine is

more effective than benadryl in these situations; at least Feinberg and Friedlaender (1947) observed benefit in 64 per cent of the cases treated with pyribenzamine whereas Feinberg (1946) had obtained such benefit in only 15 per cent of cases treated with benadryl The latter author found neoantergan helpful in eight of the ten cases in which he tried it.

Effectiveness in Asthma—Perhaps it is an understatement to say that [illegible] Fried- [illegible] enty [illegible] -five patients treated with pyribenzamine. Koelsche *et al.* (1946) reported improvement in four of twelve patients, Schwartz and Levin (1946) in eight of twenty patients, but it is notable that some of their patients reported relief from placebos; Bowen (1946) found that less than 10 per cent of his patients were helped by these drugs. Feinberg (1946) obtained only 12 per cent favorable results with benadryl in fifty asthmatic patients and with pyribenzamine in 28 per cent of 121 patients, and he furthermore pointed out that whatever benefit was derived was never comparable to the practically complete and rapid relief obtained with epinephrine administered hypodermically; he found neoantergan helpful in only one of five patients. Waldbott cited the cases of three patients who developed asthmatic attacks shortly after the ingestion of benadryl and also the case of a patient with early urticaria and asthma in whom the first dose cleared the urticaria but left the asthma unabated, however, he did cite the favorable employment of benadryl in a seven-month old infant with severe asthmatic attacks in which all other types of therapy had failed. Ratner (1947) pointed out that a drug capable of drying up bronchial secretions and producing suffocation and choking sensations might very conceivably kill a patient if used during status asthmaticus and that therefore these drugs should be used with great circumspection in cases of severe asthma; indeed McElin and Horton (1945) observed that coughing was made more difficult and that the expectorated material seemed more tenacious. Levin (1946) noted an aggravation of asthma in 3 per cent of his patients In one of his patients, when 50 mg. of benadryl was given in the office, a severe attack developed requiring the administration of epinephrine, and two other patients complained of choking up within fifteen minutes and a fourth patient had a marked aggravation of his attack, this author also stressed the fact that asthma of infectious origin was not benefited by the drug Eyerman (1946) reported two instances of idiosyncrasy to aspirin in which bronchospasm increased under benadryl and the use of adrenalin was necessitated; he also found benadryl inefficient in any severe asthmatic episode even with the oral administration of 100 mg. McGavack *et al.* (1947) obtained better results in asthma than most other workers and felt that this was due to the fact that in acute attacks they gave two to four capsules of benadryl at once with the advent of the very first symptoms

Effectiveness in Urticaria and Angioneurotic Edema.—The majority of observers find benadryl and pyribenzamine of value in over 80 per cent of patients suffering from urticaria It seems that the itching is relieved first and that then the swelling and erythema disappear, though at times swellings of unusual size remain though they no longer give rise to such active symptoms. Schwartz and Levin (1946), using benadryl, stated that in their experience in acute urticaria the wheals disappear within twenty minutes to an

about the eyes and the patient had three stools a day with considerable flatus though he had previously been mildly constipated. The recovery was very slow in this case after discontinuance of the drug, which had been taken over a period of twenty days but never in a dosage of more than three capsules per day and often only one or two.

[illegible]

reaction, which indeed not infrequently causes the use of the drug to be discontinued. Such stimulation is also observed from benadryl but apparently less often

It seems to me that Ratner (1947) was quite justified in emphasizing the potential danger in the wide-spread employment of these drugs, for certainly one cannot look upon any agent capable of causing overpowering drowsiness,

[illegible]

cost the patients their lives under certain circumstances

There is no reason to suspect that either benadryl or pyribenzamine would [illegible] came quite [illegible] er at three-hour intervals; when the lethargy and constipation in the infant became very marked after three days, it was then taken off the breast and placed on a formula and twenty-four hours later the symptoms had all disappeared.

The commonest side effects of orally administered neoantergan in Hunter's (1947) cases were sleepiness, mild headache, nausea and dizziness, but in the main these symptoms were not severe. However, one of the patients had a severe reaction with collapse, hypotension, diarrhea and intense nausea within an hour of being given 50 mg. of neoantergan subcutaneously.

With regard to the possible deleterious effects of prolonged administration of drugs of this type, we certainly do not know very much as yet. Both bena- [illegible]

should be seen once a week and that at this time a complete blood [illegible] a differential count and an examination of the urine be made. Blanton and Owens (1947) described the occurrence of fever and a marked depression of granulocytes in the peripheral blood in a woman aged seventy-three after eight weeks of pyribenzamine therapy in moderate dosage for chronic urticaria; after withdrawal of the drug and intramuscular use of penicillin the temperature dropped to normal in twelve hours and the leukocyte count and the differential percentage returned to normal in twelve days.

Epinephrine (Adrenalin) Given for Systemic Effect.—In angioneurotic edema and in urticaria the injection of epinephrine will often promptly relieve the patient, and in the fortunately rare instances of anaphylactic shock, the drug is usually life-saving. However, it is in the treatment of asthma that it is certainly most often used and the relief it effects is very frequently striking. Carryer *et al.* (1946) made the point that moderate elevation of blood pressure is not a contraindication to its use since an acutely ill asthmatic patient may receive greater trauma to his cardiovascular system from struggling in a

severe asthmatic attack than he will from the cautious use of epinephrine to halt the attack. Nevertheless, I believe that one should proceed with great

use of the drug nor is advanced age alone a contraindication. Hartman (1945) reported butanefrine in 1:500 solution equivalent to epinephrine in 1:1000 solution in cases of purely extrinsic asthma but less effective when bronchial infection was present. He found that with butanefrine, angina, nausea and pressor effects were entirely lacking and that tremor and nervousness occurred less frequently and with less severity than with epinephrine.

seconds according to the patient's tolerance usually brings relief, but it seems to me that it could also easily precipitate the disagreeable effects of overdosage.

"Slow Epinephrine" Intramuscularly.—The Council-accepted preparation is a suspension of epinephrine base in a vegetable oil. The advantage of this preparation is that for many patients the action of the drug is prolonged and therefore injections do not have to be made so frequently. The initial dose for adults should be 0.2 cc. and certainly not more than 0.5 cc. and larger dosage should subsequently be given only with great caution because 1 cc. of this preparation is equivalent to 2 cc. of the ordinary aqueous 1:1000 solution. Rackemann (1943) listed the following reactions that he said not infrequently follow these injections: headache, nausea, vomiting, cyanosis, dyspnea, chills, perspiration, insomnia, extreme tremor, nervousness, vesicular urticaria, swelling and edema of the forearm. In most cases these symptoms have manifestly been due to merely excessively rapid absorption of epinephrine, but it is not certain that the oil in which the drug is suspended may not rarely cause an allergic reaction of its own. All who have experience with this preparation counsel that it is to be given intramuscularly and not subcutaneously; one should be certain of not being in a blood vessel before injecting. Dorwart's (1940) experience, in which he was able to control the

epinephrine in gelatine, previously developed by others, and found it "useful"; unfortunately this preparation requires to be kept in the refrigerator.

Epinephrine Inhalation.—The use of epinephrine by inhalation, with ab-

about the eyes and the patient had three stools a day with considerable flatus though he had previously been mildly constipated. The recovery was very slow in this case after discontinuance of the drug, which had been taken over a period of twenty days but *never in a dosage of more than three capsules per day* and often only one or two.

Other side effects of these drugs are dilated pupils, headache and dry mouth Friedlaender (1946) noted that pyribenzamine in large doses produces *symptoms of cerebral stimulation*, and many individuals have since observed this reaction, which indeed not infrequently causes the use of the drug to be discontinued. Such stimulation is also observed from benadryl but apparently less often.

It seems to me that Ratner (1947) was quite justified in emphasizing the

impunity. Weil (1947), and Borman (1947), among others, have reported cases of such completely incoordinated and irrational action as might easily have cost the patients their lives under certain circumstances.

There is no reason to suspect that either benadryl or pyribenzamine would have any deleterious effect on the coronary circulation.

Ratner (1947) cited an instance in which a nursing infant became quite lethargic after the third dose of benadryl given to the nursing mother at three-hour intervals; when the lethargy and constipation in the infant became very marked after three days, it was then taken off the breast and placed on a formula and twenty-four hours later the symptoms had all disappeared

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effective, and in moderately severe or mild cases the result seems to depend upon whether or not the patient happens to be susceptible to the drug's action, whereas practically all persons respond favorably to epinephrine The chief advantages of ephedrine are that it can be given by mouth and that its effect is relatively long-lasting. Herxheimer (1946) has pointed out that many patients do not respond to the "average" ephedrine dosage of 1/4 to 1 grain (15 to 60 mg) but that they will react well to doses of the order of 2 to 3 grains (0 12 to 0 18 gm.), and usually without any toxic signs or symptoms However, ephedrine tolerance is quickly acquired and if the drug is given three or more times daily it may lose its effect in as short a period as three or four days regardless of the dosage employed But the responsiveness seems to be quickly regained if the patient is taken off the drug for three or four days. Herxheimer therefore suggested that intermittent treatment with the primary effective dose is to be preferred to continuous administration The frequent and oftentimes marked though not serious nature of the side actions of ephedrine preclude its use altogether in a large proportion of patients: nausea, vomiting, sweating, bladder irritability, urinary retention, skin eruptions, dysmenorrhea, palpitation, vertigo, tremor, general nervousness and apprehension, insomnia, and so on. Caffeine and nicotine in most instances definitely increase the severity of the symptoms. The greatest possible care should be exercised to avoid giving epinephrine and ephedrine in a way that might permit their effects to overlap The barbiturates, especially amytal, are much used to counteract the ephedrine side-actions

I do not find any evidences in the literature that racephedrine has any distinct advantages over the older drug.

Many observers have reported the successful use of ephedrine by mouth in hay fever, subject to the same qualifications as to dosage and undesirable side-effects that apply in asthma.

Aminophylline in Asthma.—The efficacy of the intravenous administration of aminophylline for the relief of attacks of bronchial asthma has been amply shown since introduction of this measure by Efron in 1936. Aminophylline is a feebly acid salt that may be easily thrown out of solution when it encounters the alkaline reaction of the blood, hence in order to avoid a reaction characterized by a sharp fall in blood pressure the agent must be injected very slowly intravenously Waldbott (1945) says that the peculiar sensation in the face and mouth typical of aminophylline's action has caused patients to faint but that in his experience with a very large number of injections he has never seen any serious ill effects. He makes his injection very slowly using only 1/3 to 1/2 of the 3-3/4 grains (0.24 gm) ampule. Other reactions to aminophylline are hyperpnea and nausea and vomiting; Merrill (1943) reported three deaths but all the patients had heart disease. Kahn (1947) says that aminophylline may be given intravenously two, three, or four times daily without harm for days and even for weeks; he records a case in which 196 injections were administered in eighty days He has observed also that the administration of a small dose of epinephrine hypodermically fifteen or twenty minutes after the giving of aminophylline is often necessary to induce [illegible]

sorption occurring in the lungs, is certainly the simplest way in which the drug may be self-administered. Motor-driven nebulizers are available but the more usual practice is merely to employ a glass atomizer with a hand bulb, selecting carefully one capable of delivering a fine "nebulized" spray. The Council-accepted 1:100 solution (especially prepared for this purpose and under no circumstances to be used for injection) is employed. When using epinephrine by inhalation the spout of the nebulizer is to be placed in the mouth and directed toward the pharynx, the patient inhaling deeply as the rubber bulb is squeezed. A latent period of five minutes or longer occurs before the full therapeutic effect of nebulized epinephrine is realized, and therefore in the beginning until the patient learns his own requirements no more than two inhalations should be taken. Ratner (1947) said that he no longer uses adrenaline inhalations because the inhalation method is the most habit-forming type of epinephrine therapy and that since there is no control of dosage an unusually large amount of the drug may be absorbed with serious consequences. He quotes Benson and Perlman (1946) as having reported that in a series of a thousand chronic asthmatics death occurred seven or eight times more frequently among those who used epinephrine inhalation than among those who did not. The local vasoconstrictor action of epinephrine on the mucous membranes may also cause very severe discomfort, but *Lockey (1943) reported* [illegible] of 5 per cent of glycerin prevents this. Westcott and Gill [illegible] of the ordinary epinephrine solution [illegible] inhalation therapy. Hartman (1946) found inhalation of 2 per cent butanefrine solution almost as effective in cases of extrinsic asthma as inhalation of 1 per cent epinephrine solution; but in asthma complicated by bronchial infection butanefrine was found inferior to epinephrine.

Epinephrine Intravenously.—The intravenous injection of epinephrine is a measure that should usually be postponed as long as possible. However, Ross (1946) said that when the time comes that the patient no longer responds to the subcutaneous administration of the drug he has found that it may be given intravenously with remarkable success, though he cautioned that it should be used in this way only in cases in which injection of 1 cc. subcutaneously has ceased to produce subjective symptoms such as tremor. His technic consists in drawing 0.15 cc. of epinephrine 1:1000 solution into a tuberculin syringe and diluting to 1 cc. with sterile water; 0.05 cc. of this *dilute solution (tilt the syringe a time or two to mix!) is injected* very slowly intravenously and a pause made; at this time the patient experiences a feeling of suffocation and the bronchial spasm appears to become more severe, but Ross says that he has never seen tremor, tachycardia or palpitations. When this reaction passes off after a few seconds the contents of the syringe are injected at the rate of 0.1 cc. every thirty seconds, no further subjective discomfort being experienced and the bronchial spasm disappearing. Ross says he usually follows the intravenous injection with a subcutaneous injection to prolong the effect.

Ephedrine for Systemic Effect.—In the treatment of asthma, ephedrine has been shown to be (a) very much less reliable than epinephrine in either relieving or preventing the attacks, (b) when given by mouth, much slower (ten to thirty minutes) in exerting its effect than the older drug by injection; (c) much *longer lasting (often many hours)* in its effects when they are obtained; (d) much more toxic. In severe cases it is usually very little if at all

effective, and in moderately severe or mild cases the result seems to depend upon whether or not the patient happens to be susceptible to the drug's action, whereas practically all persons respond favorably to epinephrine. The chief advantages of ephedrine are that it can be given by mouth and that its effect is relatively long-lasting. Herxheimer (1946) has pointed out that many patients do not respond to the "average" ephedrine dosage of 1/4 to 1 grain (15 to 60 mg) but that they will react well to doses of the order of 2 to 3 grains (0 12 to 0 18 gm), and usually without any toxic signs or symptoms However, ephedrine tolerance is quickly acquired and if the drug is given three or more times daily it may lose its effect in as short a period as three or four days regardless of the dosage employed. But the responsiveness seems to be quickly regained if the patient is taken off the drug for three or four days Herxheimer therefore suggested that intermittent treatment with the primary effective dose is to be preferred to continuous administration The frequent and oftentimes marked though not serious nature of the side actions of ephedrine preclude its use altogether in a large proportion of patients. nausea, vomiting, sweating, bladder irritability, urinary retention, skin eruptions, dysmenorrhea, palpitation, vertigo, tremor, general nervousness and apprehension, insomnia, and so on Caffeine and nicotine in most instances definitely increase the severity of the symptoms. The greatest possible care should be exercised to avoid giving epinephrine and ephedrine in a way that might permit their effects to overlap. The barbiturates, especially amytal, are much used to counteract the ephedrine side-actions

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this combined therapy the patients were advised to use a suppository morning and night regardless of how they felt. It was found that 93.5 per cent of the forty-seven patients were helped by the use of this suppository, both frequency and severity of attacks being reduced. However, the authors stated that these were mild and moderately severe ambulatory cases of asthma and that in severe attacks they felt that aminophylline must be given intravenously. A number of patients complained of slight itching or burning from the suppositories and in several instances there were cramps and diarrhea; much of the difficulty was overcome by lubricating the suppository with an anesthetic ointment such as nupercainal.

Aminophylline may also be introduced rectally through a tube, though

inhalation by a special device, a combined steam generator and aerosolizer.

Expectorants in Asthma.—Since the bronchi may be blocked with accumu-

most consistent value are the fluid extract of ipecac and the iodides. Ratner (1947) says that if epinephrine is not giving the expected relief, ipecac will cause forceful vomiting with release of the plugs and relief so speedy as at times to be truly dramatic. He feels that ipecac in causing nausea, retching and vomiting induces a peristaltoid action in the trachea and releases the obstructing plugs through what he calls "tracheal vomiting." To infants and young children he gives ½ to 1 teaspoonful (2 5 to 5 0 cc.) of the syrup of ipecac, and if this does not cause vomiting he gives 2 teaspoonfuls (10.0 cc.) In older children and adults repeated doses may be given until the desired result is achieved. The ipecac is followed by warm water.

The iodides, being partially eliminated in the bronchi, presumably liquefy the secretions as the result of a slight irritation effected on the mucous membrane Tuft and Levin (1942) made a comparative study of iodides given intravenously and orally, bronchoscopy being performed on each patient and specimens of secretions being obtained at regular intervals following the giving of the drug. They found that intravenous administration has little if any advantage over the oral route Carryer et al (1946), of the Mayo Clinic, offer the following palatable iodide prescription:

℞	Potassium iodide	℥ss	15 0 cc.
	Fluid extract of lobelia	♏xx	1.2 cc
	Fluid extract of hyoscyamus	♏xx	1.2 cc.
	Glycerin	ʒv	20 0 cc.
	Simple elixir to make	℥viii	240 0 cc.

Label: 1 teaspoonful in water three times daily after meals.

For children a saturated solution of potassium iodide is more easily administered than the above prescription. Bronchoscopy must occasionally be resorted to for the removal of sticky plugs from the bronchi.

sider even a single dose of the drug taboo under any circumstances, the reason being that morphine causes constriction of the bronchioles, diminution in tracheal ciliary movement and depression of the respiratory center, these actions have undoubtedly caused death in numerous asthmatic patients. Unger (1945) recently reported two such instances and Ratner (1947) goes so far as to express the opinion that most asthmatic deaths are directly or indirectly due to the use of this drug.

It seems to me that, despite the skepticism with which it is viewed by some allergists, demerol should be a boon to the asthmatic because it relaxes the bronchi To be sure this drug does not produce sleep with as great regularity as does morphine, but it does cause sleep in about 50 per cent of instances and

than is morphine.

Extremely severe attacks of asthma may be relieved and status asthmaticus may be interrupted by the colonic administration of ether and oil in equal parts. Kahn (1937) allows twenty minutes for the administration of 5 to 7

mixture two and even three times daily Maietta (1942) made a preliminary report on the intramuscular injection of the contents of an ampule containing 1 cc of ether and 1 cc of peanut oil; in status asthmaticus such injections were made every four to six hours, and in another group of long-standing asthmatics injections one or twice weekly seemed to effect a reduction in the

symptoms for days and even weeks, and he also considers it noteworthy that refractoriness to epinephrine was lost Shulman (1942) made a preliminary

this dosage. Shulman noted some personality improvement and suggested that dilantin might find its best usefulness when a strong psychogenic factor exists I have heard nothing recently of these latter two procedures. Five to 10 grains (0.3 to 0 6 gm.) of aspirin, administered together with a hot whiskey toddy, is a potent mixture that will oftentimes conquer even severe paroxysms of asthma (Duke, 1928). The first dose of the aspirin should be very small, however, because some asthmatics are hypersensitive (*i e.*, have an allergic reaction) to the drug, indeed, most allergists show signs of distress at the mere mention of aspirin.

in extremis, have become so insensitive to the action of epinephrine as hardly to respond to the drug at all. His argument was that the dyspnea in these cases is not due to oxygen want, or to the presence of carbon dioxide in excessive quantity, but to the fact that in the presence of plugged bronchi, the muscles of respiration are exhausted to the point of impending cessation of activity in their effort to maintain the normal velocity of air movement demanded by the mechanism reflexly controlling respiratory activities. His proposal of helium as a new therapeutic gas was based on the conception that its decreased specific gravity in relation to nitrogen (it is only one-seventh as heavy) would make a helium-oxygen mixture easier to breathe than a comparable nitrogen-oxygen mixture such as occurs in air. When put to the test the idea was soon proved to be correct, for patients were not only quickly brought out of their serious condition but they also regained in considerable measure their ability to obtain the usual relief from epinephrine. The mixture (helium, 80 per cent; oxygen, 20 per cent) has since been successfully used by many observers. Barach and Cromwell (1940) concluded that 90 per cent of their eighty-four patients with severe intractable asthma were decisively benefited by the regimen; in Barach's most recent reports (1943–44) he ascribes even better results to the combined use of helium-oxygen and aminophylline by rectum

Cooke (1943), objecting to the "prohibitive" cost of helium, finds oxygen introduced alone through the nasal catheter entirely satisfactory, but Basch *et al.* (1941) found the inhalation of oxygen alone greatly to increase both the viscosity of the sputum and its content of solid substances. Ratner (1947) makes the point that under no circumstances should the patient be put into an oxygen tent for the reason that during an asthmatic seizure he naturally feels that he is being smothered and indeed may even benefit from the gentle breeze from an electric fan.

Treatment of Cough.—Glaser (1946), who feels that an appropriate cough mixture for an asthmatic child should contain ephedrine (unless the child has an idiosyncrasy for this drug in which case neosynephrine or propadrine will have to be substituted), says that his favorite cough mixture under such circumstances is the following:

℞	*Codeine sulfate*	gr. iv	0.25
	Ephedrine sulfate	gr vi	0 4
	Glycerin	ʒii	8 0
	Syrup of hydriodic acid	℥ii	60 0
	Syrup of cherry to make	℥iv	120 0
	Label Teaspoonful in water every three or four hours		

This dosage may be given a child of three years and upwards but must be reduced proportionately for smaller children. It should be noted that the syrup of cherry here is not the syrup of wild cherry more frequently employed in prescriptions; Glaser uses the syrup of cherry in preference because he finds that children like it much better and he says that if the pharmacist does not have it the readily available soda fountain syrup of cherry may be [illegible]

flex in asthma.

Inhalants.—In mild cases of asthma the inhalation of the smoke from an ignited mixture of stramonium and a nitrate may be resorted to once or

several times during the night; there are available a number of commercial asthma powders and cigarettes, but the following is more economical:

℞ Sodium nitrate	℥ss	15 0
Powdered anise	℥ss	15 0
Stramonium	℥j	30 0

Label A teaspoonful to be ignited and the smoke inhaled.

Carryer *et al.* (1946) condemned the inhalation of such fumes because, while temporary relief may be thus obtained, the bronchial irritation produced

patients are debilitated, *i.e.*, depleted of body weight and strength, and that it is really quite an academic point whether the depletion precedes the asthma or vice versa, since the definite indication is to attack the state itself and *"build up" the patient as a primary consideration looking toward the relief* of his asthma. Sometimes rest alone will turn the trick, or the improvement of the dietary, or the general hygiene and regulation of the daily activities In short it is the depleted and devitalized condition of the patient that requires primary attention, though this may seem at first to have nothing directly to do with allergy. However, since such treatment of the patient as a whole is sometimes highly rewarded it is certainly of great importance

really fundamental discoveries with regard to the nature of man and his reactions to his environment.

Under this head of general measures one should note that in some individuals with extrinsic asthma the sensitivity seems to be so relatively slight that the attacks occur only when the patient has acquired a common cold, so that in such instances the obvious indication is to prevent the contraction of cold by whatever methods are possible (what are the methods?).

Rackemann (1947) has also written of asthma that disappeared when divorce was arranged, when the menopause was finally completed, when the obesity was treated, or when simple directions about decent and calm living were followed. In some instances in his experience, more often in men than in women, the removal of the focus of infection has resulted in the disappearance of asthma, and very occasionally this happy result has followed sinus operations, though he is careful to state that in a larger number of cases the sinus operation seemed to precipitate the development of severe asthma.

Psychotherapy.—It is interesting to find Landau (1946) saying that a psychiatric consultation is desirable in every case of chronic urticaria since even if other factors are clearly playing a part there are likely to be some

hand when one will have to recognize that in some at least of the allergic states, perhaps principally in asthma, there may be abnormal psychoneurogenic elements in the background that can only be effectively handled by psychiatrically trained specialists.

Penicillin.—Miller (1947) has well reviewed the subject of the use of penicillin in intractable asthma, *i.e.*, in cases in which there had failed to be a response to prolonged efforts at control of extrinsic allergic factors. He concluded that in such cases of so-called intrinsic asthma the results from the use of penicillin are certainly variable and that the use of the agent can by no means be considered a panacea. He said that more properly penicillin should simply be regarded as an agent for the treatment of infectious processes and that as such it seems to be effective in a small proportion of cases of apparent bacterial origin. As examples of about what is to be expected one may cite Miller's own experience with twenty-nine patients. Eleven of these twenty-nine patients showed an excellent response while receiving penicillin in that they became symptom-free or nearly so, eleven cases showed some improvement, and seven cases were not helped at all. Another recently reported series is illustrative: Segal and Ryder (1947) treated twenty-two patients with severe chronic infective bronchial asthma, using aerosolized penicillin, and found the therapy generally disappointing although striking improvement was occasionally observed. In all of Segal and Ryder's patients, control of the primary bronchial infection with intramuscular penicillin and oral sulfonamides had previously proved equally disappointing. Perhaps one should also cite the experience of Engelsher (1946), whose patients were treated with penicillin for from two to four weeks: some grew worse as a result of irritation from the penicillin aerosol, and some developed dermatitis and were unable to continue after two weeks therapy; of those who did continue for the full period of four weeks only 15 per cent thought that they ... per cent

were defin

muscular

Dietetics.—The whole gamut of dietary experiments has been run in the allergic diseases but nothing has come of this in the way of direct therapy. However, the importance of special procedures in the attempt to identify ... I shall now outline the methods.

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case is based upon the use of "elimination" diets (Table ...), ...sting of foods that have been found by experience rarely to cause symptoms Rowe says that Diets 1 and 2 may be prescribed separately or together, modifying them by ... known

... Diet 3

... y indi-

cations of milk sensitization, other foods being gradually ... ; effect of each watched. On whatever diet is chosen, the patient should be encouraged to eat enough to prevent loss of weight, the physician substituting similar foods for any causing disturbance. If symptoms are relieved, one or two vege- ... may be added the second week, and during succeeding weeks

Soybean milk (Sobee) is sometimes used as a substitute in patients sensitive to cow's milk; Cemac contains beef and vegetables.

With full cooperation it is said that patients can usually be got up to satisfying and nutritionally correct diets in a few weeks, but sometimes the process requires months or even years That it is often extremely difficult to maintain nutrition in patients sensitive to many things has been emphasized by Alvarez

TABLE 7.—ELIMINATION DIETS FOR THE TREATMENT OF FOOD ALLERGY (ROWE)

Diet 1	Diet 2.	Diet 3.	Diet 4.
Rice	Corn	Tapioca	Milk*
Tapioca	Rye	White and sweet potato	
Rice biscuit	Corn pone	Lima bean potato bread	
Rice bread	Corn rye muffin	Soya bean lima bean bread	
	Rye bread		
	Rye crisp		
Lettuce	Tomato	Beets	
Spinach	Squash	Carrots	
Carrot	Asparagus	Lima beans	
Beet	Peas	String beans	
Artichoke	String beans	Tomato	
Lamb	Chicken	Beef	
	Bacon	Bacon	
Lemon	Pineapple	Lemon	
Grapefruit	Peaches	Grapefruit	
Pears	Apricot	Peaches	
	Prunes	Apricot	
Cane sugar	Cane sugar	Cane sugar	
Wesson oil	Mazola oil	Olive oil	
Olive oil	Wesson oil	Wesson oil	
Salt	Salt	Gelatin	
Gelatin	Karo corn syrup	Salt	
Syrup made of maple sugar or cane sugar, or cane sugar flavored with mapleline or maple sugar	Gelatin	Olives	
Olives		Maple syrup or syrup made with cane sugar flavored with maple	
Pear butter			

* Milk should be taken up to 2 or 3 quarts a day. Tapioca cooked with milk and milk

(1930) ...

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	Rye crisp		
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Spinach	Squash	Carrots	
Carrot	Asparagus	Lima beans	
Beet	Peas	String beans	
Artichoke	String beans	Tomato	
Lamb	Chicken	Beef	
	Bacon	Bacon	
Lemon	Pineapple	Lemon	
Grapefruit	Peaches	Grapefruit	
Pears	Apricot	Peaches	
	Prunes	Apricot	
Cane sugar	Cane sugar	Cane sugar	
Wesson oil	Mazola oil	Olive oil	
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Olives		Maple syrup or syrup made with cane sugar flavored with maple	
Pear butter			

* Milk should be taken up to 2 or 3 quarts a day. Tapioca cooked with milk and milk sugar also may be taken

Note Wesson (cotton seed) oil is included in all diets With allergy to cotton seed as shown by skin test or history this must be excluded and a cotton seed oil shortening such as Crisco must not be used If allergy to cane sugar is suspected, beet sugar or corn glucose may be used.

effects of "dieting" must not be overlooked. This is a type o specific therapy that, because of its freedom from dangers, its relative simplicity and its inexpensiveness, deserves a wider trial than it has perhaps been given—if only patients were not so prone to snitch forbidden foods! Alvarez (1946) h

repeated attacks of migraine or eczema will have to stay on an elimination diet for a somewhat longer period of time, but he feels that the diet will in these cases have to be liberalized so as to make life more worth living during such a period.

Food Diaries.—Many allergist find this the easiest and most efficacious method of determining the food or foods to which the patient has become sensitized. It consists merely of having the patient keep a complete record of every

in persons who are very active.

Topical Applications in Hay Fever and Vasomotor Rhinitis.—I think the opinion of Kelley (1945), as expressed in a Cornell Therapeutic Clinic, will give a fair cross section of the opinion of men experienced in the use of the sympathomimetic amines for their topical action on the nasal mucous membrane. He said of epinephrine (adrenaline) that it is rapid and brief in action, and causes various degrees of sneezing, watery nasal discharge and tearing, all of which may persist for a few hours to a day or more. He said that he formerly used ephedrine extensively but has now given it up in favor of the more recent amines that have come into vogue. The immediate after-effects and duration of reaction of ephedrine are less pronounced than those of epinephrine, its vasopressor effects and duration of action comparing favorably with those of neosynephrin; it may be used in the form of a solution, in oil, spray or as drops. But he found that if ephedrine is used for a week or more the patient may complain of nervousness, restlessness, and perhaps insomnia, and that some individuals develop local sensitivity to the agent, the nose becoming irritated and the mucous membrane blotched with small red and dry excoriations. He said that he used benzedrine for a short time only. Its action is rapid but of relatively short duration and the after-effects of irritation and nasal congestion are rather marked and of prolonged duration; he said that the patient is likely to resort to the frequent administration of this drug with

just long enough to discover that its action and reaction was similar to those of benzedrine and paredrine. Neosynephrin is preferred by Kelley to the other

amines; he employs it as a spray, as drops and occasionally in the office by tampons. Its desired effect occurs within two to fifteen minutes, its action is sustained for two hours or more, and there are fewer complaints of after-effects such as burning and nasal congestion than with the other agents. He says it may be used once or twice daily over a period of weeks with less tendency to develop local sensitivity; however, it may suddenly cause irritation and nasal

with each compression. Neosynephrin is used in a concentration of 0.25 per cent, ephedrine in 0.5 per cent aqueous, or 1 per cent oil, solution. Epinephrine of course is used in the familiar 1:1000 solution.

Among the newer amines, it is said that vonedrine when used by inhalation will give considerable relief through vasoconstriction with little or no evidence of irritation, local tissue reaction or central nervous system or cardiovascular stimulation, a 0.5 per cent solution of tuamine is considered equivalent in its vasoconstrictor effects to a 1 per cent solution of ephedrine and the duration

Alyea (1943) stated that a 0.1 per cent solution of privine is a non-toxic nasal vasoconstrictor. But in 1944, Gollom reported persistent nasal congestion in more than thirty cases following the use of privine, and the next year Feinberg and Friedlaender recorded over seventy-five cases in which symptoms of nasal congestion were aggravated or prolonged by the continued use of this agent. Thomas and Fabiano (1946) said that they had seen addiction to privine as a

onate, 1 to 5 per cent, sodium carbonate, 1/2 to 3 per cent, borax, 1 to 4 per cent. According to Cornbleet an acid lotion is sometimes more effective:
1 part of vir
line bath (1
(1 or 2 cup
which may
the type of physical allergic whose symptoms are aggravated by warming the body. Upon the other hand, sweat baths may be helpful in an occasional case.

Special Measures in Physical Allergy.—Persons highly sensitive to heat from without should avoid exposure to high temperatures as much as possible, of course, and will do well to move into a cool, dry climate. Since they are nearly always susceptible to attacks as the result of internal liberation of heat also, avoidance of physical activity is a part of the treatment as well.

Temporary relief can nearly always be obtained by the [illegible] bath. Cold-sensitive individuals can usually protect themselves by the use of adequate clothing and by taking care [illegible] selves to low temperatures when they cannot rather [illegible] the same time. For such persons swimming, whether in [illegible] natural body of water, is always particularly dangerous [illegible] have doubtless drowned through unrecognized hypersensitiveness. A hot bath is probably the quickest and simplest way [illegible] act the effects of chilling in cold-sensitive individuals. [illegible] severely enough afflicted that the mere exposure of a [illegible] body surface, such as placing the hands in tapwater, [illegible] the occupational phase of the malady may assume [illegible]

In light sensitiveness the problem is much more [illegible] adequate protection from exposure is practically [illegible] attention was called to the fact that injection of [illegible] mental animals rendered them light-sensitive, and [illegible] the observation was made in pointing out that [illegible] phyrin, a similar substance. Since this substance [illegible] wheat and in oatmeal, it would seem advisable [illegible] cereal-free diets on light-sensitive patients, even [illegible] ton and Lunsford (1952) cast some doubt on the [illegible] in this connection. The ingestion of quinine, [illegible] substances, as well as the taking of sulfonal, or [illegible] or liver insufficiency, have all been associated with [illegible] the penetration of ultraviolet rays, it has been [illegible] disodium naphthol sulfonate in solution in [illegible] may be effective.

Miscellaneous Agents.—*Histaminase* [illegible] histamine as it is liberated during the allergic [illegible] of histaminase has got nowhere clinically [illegible] since with a consideration of the agent. [illegible] the use of [illegible], a benzofuran derivative [illegible] series of patients suffering from what seemed [illegible] or hay fever though he gave their condition a [illegible] to have found the drug useful in these patients [illegible] methods employed in assessing the response [illegible] that I was unable to understand them. [illegible] the agent as beneficial in a small series of [illegible] that a great deal of work needs still to be [illegible] this agent is safe and worthwhile using. [illegible] mation and subsequent studies report of [illegible] Chemistry concerning this agent is fully [illegible] use in the treatment of allergy are not [illegible] the available evidence does not support [illegible] Of course all the vitamins have been [illegible] but it is not apparent that there is [illegible] alone or in combinations, to warrant a [illegible] Sharf [illegible] (1949) obtained [illegible] eight cases of allergic bronchial asthma [illegible] cases of nonallergic asthma, did not [illegible] report of a confirmation of these findings [illegible]

of fever therapy has been used with variable success through the years. *Potassium Chloride.*—In 1938 Bloom reported striking benefit in a small series of hay fever cases treated with this drug by mouth, dissolving 5 grains (0 3 gm.) in a glass of water and giving three or four such doses daily. There have subsequently been a few other favorable reports of potassium chloride therapy of allergies of various types, but all of the specialists in allergy have reported unfavorably. Recently, however, Stoesser and Booth (1945) found that the ingestion of potassium chloride in selected cases of chronic asthma in children led to a diuresis that was in some instances associated with an apparent inprovement in the severity of the asthmatic symptoms. *Nitrohydrochloride Acid.*—Some years ago I reintroduced this agent and am still sure that in some cases, but by no means in the majority, it is useful in relieving the symptoms both in hay fever and asthma. Rackemann (1944) confirmed this opinion with regard to asthma The following prescription is worth trying upon occasion.

℞ Nitrohydrochloric acid (*not* the dilute)	℥ivss	18.0
Distilled water to make .. .	℥iv	120.0
Label One teaspoonful in ½ glass of water, followed by another glass of water, after meals and upon retiring as late as possible		

Intravenous Procaine.—State and Wangensteen (1946) reported that eleven of seventeen patients with serum sickness were completely relieved of their symptoms, and an additional four temporarily relieved, after the intravenous administration of procaine. Six of seven patients obtained relief from urticaria and other manifestations of hypersensitiveness whether the sensitizing agents were known or not, though no patient was cured of the sensitivity state. One patient with chronic asthma was not relieved It was found that epinephrine remains the drug of choice in severe immediate anaphylactoid reactions since procaine must be administered too slowly to make its use feasible in these situations Procaine in the amount of 15 grains (1 gm.) is diluted with 500 cc. of physiologic saline solution and given intravenously by the gravity

bed level over

the patients c

Appelbaum *et al* (1946) also satisfactorily used this method of treatment in

of 200 to 300 mg of it they obtained complete and prolonged relief in forty-one of forty-five cases of severe bronchial asthma, the relief being not so prompt as under epinephrine but more lasting and unaccompanied by any effects on the systemic blood pressure Of course this agent is still in the clinical experimental stage but this first report is certainly an interesting one *Arsenicals*—Workers in the field do not seem to be able to make up their minds whether Loeffler's syndrome and tropical eosinophilia are identical entities and certainly I cannot decide the question, but I think it worthwhile recording here that in the latter malady the organic arsenicals, employed as neoarsphenamine or mapharsen or even in the form of carbarsone, have been highly effective. *Atropine.*—This is a much less valuable drug than epinephrine for use in asthma for two reasons: first, because most patients are not

markedly relieved until doses large enough to cause flushing, considerable dryness of mucous membranes, and more or less cerebral excitement are used; and second, because the majority of patients become tolerant to it much sooner than they do to epinephrine. Cooke (1943) says that atropine and belladonna are contraindicated drugs. *Dextrose-Saline.*—Rackemann (1944) says that the administration of 1500 cc. of normal saline solution containing 5 per cent dextrose usually effects relief in asthma even when the patient is in extremely great distress; this, he points out, is quite in accord with the observation of Sheldon *et al.* (1939) that a marked loss of water and sodium occurs during an asthmatic attack. *Dehydration Therapy.*—The exact reverse of the above is sometimes practiced by Cooke (1943), who says that perhaps dehydration effects relief by causing a shrinking of the bronchial wall. He places severely stricken patients on weak tea, fruit, or vegetable [illegible]

that with enough sugar and sedation, and allowing water to be taken freely, this regimen may be maintained for three or four days, and may be followed by small, frequent, salt-poor feedings. Cooke says that he also sometimes succeeds temporarily through the use of 50 to 100 cc. of sucrose intravenously, a dehydrating measure earlier suggested by Keeney—may it not be significant that he adds "especially when 0.2 to 0.4 cc. of epinephrine is added"? *Physiotherapy and Breathing Exercises.*—Various forms of hydrotherapy, baths, spa cures, ultraviolet and roentgen ray exposures have been advocated from time to time, but none merits special description here. In hay fever, diathermy is sometimes applied locally to the nasal mucosa, or special quartz rods are used to carry ultraviolet rays to the anterior and posterior nares. Perhaps the best known of the several schemes for inducing forced expiration was that employed by Hofbauer, in Vienna, between the two Wars. The thing seemed very complicated when I saw him demonstrate it, but this may be only the statement of a fact about myself; Livingstone and Gillespie were investigating the matter in England, in 1935, but I do not know what conclusion they reached. Weiser (1944), in Palestine, reported considerable success with breathing exercises in a small group of selected patients. *Surgery and Radiation.*—Despite the allegations of those who hold out for surgery in all conditions, I believe it is now the consensus among otolaryngologists that little, if anything, is to be hoped for from operative procedures in the treatment of hay fever. Cooke (1943) believes the removal of tonsils and adenoids, and sometimes sinus operations, of value in selected cases of intrinsic asthma. Woodward (1946) agrees that sinus operations are sometimes helpful, but Rackemann (1944) stated his considered opinion that such operations do not often effect a cure. Gay (1946) and Ward *et al.*, (1947), felt their results from the employment of irradiation of the nasal pharynx with radar in selected cases of intractable asthma in children justified a further detailed study of this method of therapy.

PROPHYLACTIC MEASURES IN THE ALLERGIC DISTURBANCES

The practice of "desensitizing" hay fever patients by injecting them with increasing amounts of pollen extracts at short intervals during the several months preceding their annual attack was initiated by Noon, in 1911, and has since attained a considerable vogue, though the rationale of the pro

cedure is not as yet entirely established. Perhaps the thermostable antibody of Loveless, which is demonstrable in the blood of all individuals suitably injected with allergens, offers the best avenue of approach to an immunologic explanation of the occurrences that has yet been offered. In any case, however, as pointed out by Cohen (1944), the terms "desensitization"

however, I shall be obliged to continue to offer in these pages a brief outline of how the thing is done with such methods and means as the general man has at his disposal.

rubbed in, and a drop of N/10 sodium hydroxide (4 gm. NaOH to 100 cc. distilled water) is added. An urticarial wheal with pseudopods and an erythematous area is considered positive.

Intradermal Test.—About 0.01 cc. of a liquid extract of the allergen is injected intradermally.

Patch Test.—A small area is washed and rubbed lightly with pumice stone; the allergen, either in solution or rubbed into a paste, is placed on the area and covered with a small square of cellophane and held in place by adhesive plaster. The reading is after twenty-four hours or longer.

Passive Transfer.—One-tenth cubic centimeter of the patient's blood serum is injected intradermally in a normal arm, and twenty-four hours later the suspected substance is injected or scratched into this site; the usual urticarial wheal is a positive reaction.

Reactions.—Waldbott (1945) said he has learned from experience that skin tests by the intradermal method should never be done in children below

the aged require the same meticulous care in testing and treatment as do patients of any age group. Waldbott said that for young children he finds the passive transfer test not only the most reliable for the physician but also the most appreciated by the parents and children alike.

Sensitization to drugs cannot be detected by skin tests and in cases of food allergy reactions to the offending food are not always positive nor to be relied upon. In cases of urticaria plenty of positive skin reactions will often be found, but these usually serve only to demonstrate the allergens toward which the individual is sensitive in addition to the elusive one or more that are responsible for his hives.

Leukopenic Index.—A number of years ago, there was offered a new means of detecting the food responsible for causing symptoms in cases of food sensitivity: the performance of serial white blood counts after the suspected food has been ingested under standardized conditions, a fall in the count indicating sensitivity. It was later also reported that an eosinophil increase occurs

ɔcyte reduction. Squier (1946) has presented
ukopenia is accompanied by an increased
Tuft (1946) says that extensive trial of the
ʼorroborate the findings of those who have
found it of value and that he believes it to be *seldom employed at the present* time; he finds the eosinophil index also of limited value. Nevertheless, Squier and Lee (1947) have very interestingly demonstrated the *in vitro* lysis of leukocytes when ragweed allergen was added to whole blood from patients sensitive clinically and by skin test to ragweed pollen.

Increased Pulse Rate.—Coca (1943) believes that the ingestion of food to which the patient is allergic provokes an increase in the pulse rate beyond that in the non-allergic individual, but others have not confirmed his finding to my knowledge.

Hypodermic Desensitization.—*Method.*—Of the "standard" method, New and Nonofficial Remedies (1947) has this to say: "No uniform method of standardization has been adopted. Two methods are acceptable, first, standardization by the nitrogen content of the extract, and second, standardization by the amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment, grad-

intracutaneously before the series is begun. There should be no reaction or only a minimal wheal following this test."

Timing the Injections.—The usual practice in administering "preseasonal" treatment is to give fourteen to twenty subcutaneous injections at intervals of once or twice weekly, the time of the last injection to coincide approximately with the beginning of the patient's "season," or either to antedate or postdate that time by a few days. Many attempts have been made to slow the absorption of pollen extracts by the addition to them of various substances such as lanolin, olive oil, almond oil, glycerin, formalin, gelatin, alum, etc., but none of these preparations has been entirely satisfactory. Some of them are irritating, some unstable and some non-antigenic; the oily extracts must be given intramuscularly with a long needle, the gelatin extracts must be liquefied in warm water before use, and with any of these methods a constitutional reaction is likely not to appear until the patient has left the physician's office and is not in a position to receive adequate and immediate assistance. A new method,
(1947) who applies an ice bag

dosage and thus in a patient of high sensitivity
eight to nine treatments instead of the fourteen treatments ordinarily required, thus effecting a saving of about 40 per cent in the number of visits of the pa-
during
s not
ninis-
rved.
tration of epinephrine necessitated) and no delay

Efficacy.—Expert allergists, who prepare their own extracts and are able

course of treatments must be gone through with again during the next year.

ing large numbers of hay fever patients, namely, that their percentage figures run about the same. The results, he says, are excellent in about 20 per cent of cases, good in another 60 per cent and poor in about 20 per cent. A very important question from the patient's standpoint is how many years he shall

Walker reported presumably permanent cures in 8 per cent of those treated for only one year and in 65 per cent of those treated for five years; I think that even now few observers are quite so sanguine.

Co-Seasonal Injections—Currently, it is the practice of some allergists to continue the injections throughout the season, the usual attempt being to use

injection; Cohen (1940) advised that for such patients the dose should be reduced a quarter, a third or a half Waldbott (1944) felt that in any case it is a good rule not to give another injection until the swelling from the preceding one has subsided, he thought that patients of average sensitivity should be treated every three to five days, while in individuals treated intensively before the season intervals of a week to ten days are sufficient. It should be noted, however, that Golan and Sack (1942) concluded from their comparisons of two

the specific therapy

allergists are now favoring is known as the "perennial" type, *i e.*, the persistence in the injections for as long apparently as the patient will cooperate The interval at which these injections are given varies in different practices; constitutional reactions are of course not infrequent in this type of treatment unless it is

until the advent of the following season, when weekly doses are instituted, but that patients of greater sensitiveness will not retain their tolerance for their maximum doses for as long an interval as a month. It is my impression that many men feel that upon the whole they obtain considerably better results with perennial than with conventional preseasonal care.

Co-Seasonal Injections.—When the patient does not present himself until

pollen simultaneously; usually injections are given at one- or two-day intervals

with greatly reduced dosage. Under such circumstances, Freeman (1936), of London, sometimes resorts to "rush" treatment—*i.e.*, the patient is hospitalized and eight or more pollen doses are crammed into him daily in order to get the desensitization completed in about a week. Waldbott and Ascher (1937) also reported the satisfactory use of this method in selected cases. It seems to me, however, that this "rush" method is not sufficiently free of hazards to justify the general practitioner in employing it.

Booster Injections.—Another variant in desensitization technic is that of Loveless (1944) in which patients whose responses to desensitization in previous years are well known are desensitized in a given year by the administration of short "booster" courses suited to their immunologic needs. Since in this type of therapy it is the intention to treat all patients as intensively as their tolerance permits, and as this means that generalized reactions occur not infrequently, it seems to me that the method is not one suitable for employment by the general practitioner.

Reactions to Desensitizing Injections.—Waldbott (1945) classified the treatment reactions as those due to accidental intravenous injection, backseepage due to injection next to a punctured vein into which the extract gradually ... and the reaction resulting from the giving of an overdose of the extract.

gravity of the reaction. The backseepage reaction requires one to several minutes for the symptoms to appear and is characterized by local edema that soon becomes intense and spreads quickly over the entire body; there may be ... site of the injection or a bloody suffusion under the skin, this ... cases too the symptoms are intense ... to treat reactions of the foregoing types with the utmost speed, immediately injecting 1 to 2 cc. of epinephrine subcutaneously and following this by $3\frac{1}{2}$ to 7 grains (0 2 to 0 5 gm.) of aminophylline given intravenously. Keep the needle in the vein and if the patient does not recover quickly introduce through it 0.1 to 0.3 cc. of epinephrine very cautiously (blood is withdrawn into a 10-cc. syringe containing the epinephrine, ... form).

or less itchy before it is followed by the appearance of generalized ... and respiratory symptoms; he says that no matter how large the overdose may have been there is always a lapse of from a few minutes up to an hour before generalized symptoms arise. These overdose reactions, unlike the intravenous or the backseepage ones, do not require more than 0 1 to 0.2 cc. of epinephrine unless they are unusually severe, though these small doses may have to be repeated if the symptoms do not subside; larger amounts of epinephrine are likely to produce more discomfort to the patient than the reaction itself. The application of a tourniquet above the site of injection is of considerable value, and aminophylline may be given intravenously later if indicated by asthmatic wheezing.

Rackemann (1947) has well emphasized the fact that the level of absolute tolerance appears to be at a point more or less fixed for each patient and that ... recognized the danger of incurring a general systemic ... w this level; but he also pointed ... tient from year to year.

Engelsher (1945) said that Duke's method of adding epinephrine to each

tolerates pollen injections as well as or even better than the non-pregnant individual, however, that the possibility of inducing miscarriage as a result of a severe systemic reaction exists was exemplified in the case report of Francis (1941).

Oral Desensitization.—*Pollens.*—Oral pollen desensitization is suggested *from time to time but it is still the opinion of the vast majority of leading*

there are people who have gastro-intestinal discomfort while taking oral pollen, but Thiberge (1945) felt that if the precaution is taken of using enteric-coated pollen pills the gastric symptoms may be avoided Landau and Gay (1945) treated a small group of hay fever patients with ragweed pollen propeptan (see below) with very poor results

Peptones (*Propeptans*) —Both the French and English schools had for some time been using peptones by mouth in cases of food allergy with indifferent results, when Luithlen, in 1920, showed that the fault probably lay in the use of preparations that were not truly specific. Urbach, who very actively carried on the investigations in Vienna and continued them in this country until his untimely death, demonstrated that the treatment is worthless unless the exact peptone to which the patient is sensitive is employed, for example, if an individual cannot eat chicken, the peptone to be used must be made from the

that the method is hardly practicable in frequently fed infants

cause its simplicity and inexpensiveness seem to warrant its being given a trial by general practitioners The proposers of the method, and more recently Edwards (1940), have reported its successful employment in small series of cases and there are numerous physicians with single case successes; specialists in allergic diseases are notably reticent in the matter, though Tuft (1946) has expressed himself as feeling that oral desensitization by the protein dilution method is more likely to be helpful than specific desensitization by the hypo-

dermic method—which is, as a matter of fact, not saying much, for the latter method is practically never employed by allergists nowadays in cases of food allergy. The protein dilution method consists in attempting to desensitize

(Table 8) indicates the procedure in instances of sensitization to egg only; Keston *et al.* offer slight variations in dilutions in connection with the other food-

TABLE 8.—PROTEIN DILUTION METHOD OF DESENSITIZATION IN FOOD ALLERGY (KESTON, WATERS AND HOPKINS)

Directions —Beat an egg so that yolk and white are well mixed; then add the prescribed amount of egg to ordinary water and mix well Take 1 teaspoonful of the solution once a day unless otherwise directed Throw away the rest of the solution Make up a fresh solution every day. Use a dilution of the same strength every day for four days.

Mix 1/4 teaspoonful egg with 2 quarts of water. Take 1/4 teaspoonful.
Mix 1/4 teaspoonful egg with 3 pints of water. Take 1/4 teaspoonful
Mix 1/4 teaspoonful egg with 2 quarts of water Take 1/2 teaspoonful.
Mix 1/4 teaspoonful egg with 3 pints of water. Take 3/4 teaspoonful
Mix 1/4 teaspoonful egg with 2 quarts of water Take 1 teaspoonful
Mix 1/4 teaspoonful egg with 3 pints of water.
Mix 1/3 teaspoonful egg with 2 quarts of water.
Mix 1/2 teaspoonful egg with 3 pints of water
Mix 1 teaspoonful egg with 2 quarts of water.
Mix 1 teaspoonful egg with 3 pints of water.
Mix 1 teaspoonful egg with 1 quart of water
Mix 2 teaspoonfuls egg with 3 pints of water
Mix 1 teaspoonful egg with 1 pint of water.
Mix 2 teaspoonfuls egg with 1 1/2 pints of water
Mix 1 teaspoonful egg with 1 cup of water.
Mix 2 teaspoonfuls egg with 1 1/2 cups of water
Mix 1 teaspoonful egg with 1/2 cup of water.
Mix 2 teaspoonfuls egg with 1/4 cup of water.
Mix 1 teaspoonful egg with 1/4 cup of water
Mix 1 teaspoonful egg with 3 tablespoonfuls of water.
Mix 1 teaspoonful egg with 2 tablespoonfuls of water
Mix 2 teaspoonfuls egg with 3 tablespoonfuls of water.
Mix 1 teaspoonful egg with 1 tablespoonful of water
Mix 4 teaspoonfuls egg with 3 tablespoonfuls of water
Mix 2 teaspoonfuls egg with 1 tablespoonful of water.
Take 1 teaspoonful of raw egg.
Take 1 1/2 teaspoonfuls of raw egg.
Take 2 teaspoonfuls of cooked egg.
Take 3 teaspoonfuls of cooked egg.
Take 4 teaspoonfuls of cooked egg.
Take 1/2 cooked egg
Take 3/4 cooked egg
Take a whole egg.
After this eat at least 1 egg every few days.

stuffs they have successfully used, but since they found greater difficulty in

amount of the ol-
complete absence
ttle difficulty.

Bacterial Vaccines.—Some years ago a number of authors were able to report results with bacterial vaccines that were quite comparable with those obtained by the institution of specific desensitization. The usual method was to prepare vaccines from pure cultures of organisms obtained from the thick

vaccines are of little if any value. In 1939, however, Stevens and Crump independently studied the use of vaccines in asthmatic children and felt that some good results were obtained in these young patients. Crump prepared her vaccine from material removed through the bronchoscope Cooke (1943) employs autogenous vaccine in selected cases but recognizes that too large dosage may induce a severe status asthmaticus.

Histamine.—Histamine has been used in various allergic affections for a number of years throughout the world, but there has not been agreement regarding its efficacy In this country Thiberge, in 1935, made the astonishing claim of improvement in 95 per cent of his treated asthmatics. Farmer (1941) reported more conservatively on twenty-three patients who had either asthma

mine phosphate, giving two or three injections weekly in the beginning and increasing the dose 50 per cent each time, later the injections were spaced at five-, seven-, ten-, fourteen- and twenty-one-day intervals, depending upon the patient's tolerance and the results achieved; the maximum doses, not often employed, were 50 to 75 gamma The precautions to be taken are the same as in specific desensitization, but systemic reactions have occurred very rarely.

repeating his dose as often as was necessary to control the symptoms, but preferably when the stomach was empty. I have seen no recent reports of the use of histamine but believe it to be still on trial by a large number of practitioners.

working hypothesis for the production of compounds of this sort is very

if the specificity of this artificially produced antigen were determined by the histamine contained in the molecule, we might expect through the administration of such an agent to neutralize the histamine released by the antigen-antibody reaction and thus prevent the occurrence of allergic phenomena. An azoprotein compound of this sort was produced by Fell *et al* (1943)

and introduced for clinical trial under the title of hapamine. However, in sampling the clinical experience of allergists, the Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy obtained information indicating that those who have given hapamine a fair trial either have found it totally ineffective or have been able to attribute whatever measure of effectiveness it had to its non-specific action. Feinberg (1946), reviewing the subject, said that his own personal experience was in agreement with this opinion. Ratner (1947) says that hapamine proved unsound not only because it did not produce any immunity but because it induced sensitivity to the new hapten antigen in a number of instances.

Pollen Filters and Air Conditioning.—There seems to be no doubt that hay fever sufferers are greatly, sometimes completely, relieved during their sojourn in a room that is "air conditioned"; in more severe cases some one or other of the several types of filters that will completely remove the pollen from a room may be needed Such equipment is relatively expensive of course and usually requires considerable care to be maintained in satisfactory operation. The provision of an adequate number of pollen-free rooms in hospitals, without excessive charge for their occupancy, would be a great boon to many sufferers.

Masks.—Nowadays one occasionally encounters an individual on the street wearing a mask covering the mouth and nose. I know of no controlled study of the efficacy of such masks but should think it would be difficult to prevent leaks between them and the skin and that furthermore sufficient pollen might enter through the unshielded eyes to induce symptoms in some instances.

Desensitizing Measures in Physical Allergy.—Duke reported that he was able to desensitize some cold-sensitive individuals by accustoming them to plunge into a cold bath for a few seconds every morning; in others he employed a rapid ice rub all over the body. In other instances he prevented an early morning attack by warming up the patient thoroughly by a hot bath at midnight. Horton *et al.* (1936), at the Mayo Clinic, stated that the average cold-sensitive patient can be adequately desensitized by having him immerse a hand in water at 50° F. for one to two minutes twice a day for three to four weeks; in some instances they also succeeded by starting with the water at 65° F. and decreasing the temperature to 45° F. for increasing periods.

DEFICIENCY DISEASES

SUBCLASSICAL DEFICIENCY STATES

The major [illegible]
to eat in ter [illegible]
bad dietary [illegible]
affairs. The [illegible]
enough to recognize and usually to treat, but leaders in this field of study have pointed out two facts: (a) that deficiency in a single nutritional factor is rare, *i e.*, most of the syndromes as seen by the practitioner are multiple and not single deficiencies; and (b) that the classical deficiency diseases all have their subclassical phases It does not simplify matters either that in the current state of our knowledge the diagnosis of a subclassical deficiency must be made in practically all instances without the aid of the laboratory or the use of instruments of precision In our own country most of the gross deficiency exists in the South, but Jolliffe (1945) said that a recent survey under the auspices of the National Research Council revealed that a significant fraction of the American population in all parts of the country and in all economic groups fails to include in its daily dietary all the basic foods considered essential for optimum nutrition. The reader will probably be surprised in studying Table 9, published by Bing, of the Food and Nutrition

TABLE 9—A PROBABLY ADEQUATE DIET

[illegible]

vitamin A

Cereals and bread, and butter and other fats These are the energy foods. In selecting them it is well to choose those items which contribute additional food values Thus the cereal products ought to be whole grain or enriched Fats ought to be butter which contains vitamin A. If oleomargarine is used for economy, then it would be well to select that which supplies added vitamin A.

(Bing, 1943)

Board of the National Research Council, to see just how much food, and of what quality, must be taken in order to obtain a "probably adequate" diet. Of course the correction of the dietary inadequacies of whole populations is a task that does not lie within the province of the practicing physician, but it is very much the physician's job to recognize and treat deficiency states in individuals who are his patients. Of course here as in other types of dis-

ease, the thing which most facilitates diagnosis is to suspect the presence of the entity. Spies (1944) has pointed out that information in regard to income and food resources is often of value in determining the adequacy of the individual diet. If the amount of money available for food is small and if the patient has no food resources such as a garden, cow, or chickens, it is almost certain that his diet has been inadequate He says that he and his

TABLE 10—CONDITIONING FACTORS THAT MAY CONTRIBUTE TO NUTRITIONAL FAILURE

I. *By Interfering with Food Intake*
1. Gastro-intestinal diseases as:
   - Acute gastro-enteritis
   - Cholecystitis and cholelithiasis
   - Peptic ulcer
   - Diarrheal diseases
   - Carcinoma of stomach and esophagus
2. Food allergy
3. Mental disorders as:
   - Neurasthenia
   - Neurosis
   - Psychoneurosis
   - Psychosis
4. Operations and anesthesia
5. Infectious diseases associated with anorexia
6. Loss of teeth
7. Heart failure (anorexia, nausea, and vomiting by visceral congestion)
8. Pulmonary disease (anorexia, vomiting due to cough)
9. Toxemia of pregnancy (nausea and vomiting)
10. Visceral pain (as in renal colic, and angina that reflexly produces nausea and vomiting)
11. Neurologic disorders which interfere with self-feeding
12. Migraine

II. *By Interfering with Absorption*
1. Diarrheal diseases as:
   - Ulcerative and mucous colitis
   - Intestinal parasites
   - Intestinal tuberculosis
   - Sprue
2. Gastro-intestinal fistulas
3. Diseases of liver and gallbaldder
4. Achlorhydria
5. Carcinoma of the stomach

III. *By Interfering with Utilization*
1. Liver disease
2. Diabetes mellitus
3. Chronic alcoholism

IV. *By Increasing Requirement*
1. Abnormal activity, as associated with prolonged strenuous physical exertion with lack of sufficient sleep or rest, delirium and manic-depressive psychoses
2. Fever
3. Hyperthyroidism
4. Pregnancy and lactation

V. *By Increasing Excretion*
1. Biliary or gastro-intestinal fistula
2. Perspiration
3. Loss of proteins in nephritis and nephrosis
4. Polyuria, as in.
   - Diabetes mellitus
   - Diabetes insipidus
   - Long-continued excessive fluid intake as in urinary tract infections
5. Lactation

VI. *By Therapeutic Measures*
1. Therapeutic diets, as in·
   - Sippy regimen
   - Gallbladder disease
   - Anti-obesity diets
2. Antacids
3. Mineral oil
4. Infusions
5. Diuretics
6. Fever therapy
7. Paracentesis and thoracentesis

(Jolliffe and Smith, 1943)

associates have found that many families have a good dietary immediately after payday but that it gradually tends to become poorer as the money diminishes, insurance payments, illness and other factors making demands on the income often seriously affect the quality of the dietary. Emotional factors likewise tend to affect the food intake, especially in women who worry their children and household problems or are working outside their homes and attempting to take care of their family and housework as well

Such individuals will often fail to eat a proper diet even when it is available. In such instances, though only one individual may present as the patient, deficiency diseases of either a classical or subclassical degree are likely to be found in all the members of the family.

Spies (1944) says he suspects nutritional deficiencies in the following groups:

(1) Those who for any reason have a food intake below that recommended for an adequate diet.

(2) Persons who are chronically addicted to alcohol.

(3) Persons who have an organic disease that might interfere with the absorption or utilization of food or might increase food requirements. One might add also, as do Jolliffe and Smith (1943), see Table 10, conditions in which nutrients are lost by increased excretion or through the employment of certain therapeutic measures

(4) Persons whose physical exercise is increased but whose diet is of borderline inadequacy

As a deficiency disease develops there occur functional disturbances arising from every part of the body and giving a complex clinical picture with a great variety of symptoms possibly existing for months or years before characteristic lesions appear. Spies says that their group is particularly concerned with the following symptoms as suggesting the possible development of a deficiency state loss of weight and strength, headaches; dizziness; burning sensations of the skin on various parts of the body, roughness and dryness of the skin, burning of the eyes, blurring of vision, lacrimation, photophobia and night blindness, burning and cramping of the stomach; burning of the tongue and lips, redness, swelling and ulcerations of the tongue and mucous membranes of the mouth, increased salivation, diarrhea; burning and cramping of the feet and legs Central nervous system disturbances including insomnia, general nervousness, loss of memory, apprehension and hypersensitive emotional reactions are common symptoms that may appear early in the development of a deficiency state These symptoms tend to come and go and with each recurrence become more severe until definite clinical evidence of one or more deficiencies appears

THERAPY

Once the diagnosis has been made the conditions which have brought about the deficiency should be overcome if possible. Symptomatic treatment and the treatment of coexisting diseases should be undertaken The patient should be put on a well-balance diet of 3000 to 4000 calories with liberal amounts of minerals and vitamins and a daily supply of 120 to 150 gm. of protein. Cayer (1946) offers the following table (Table 11) of foods classified according to their value as sources of the principal vitamins Spies and Morey (1946) said they have become increasingly impressed by the fact that nutritive failure cannot be permanently corrected by the administration of a single chemical substance if the diet continues to be inadequate. In their experience clinical evidence of protein deficiency is often absent or obscure in these subclassical cases but they have found that such deficiency is often common among persons who subsist upon inadequate diets and that these individuals respond well to protein derived from milk, meat or eggs.

Of course at times in treating the subclassical deficiencies it is necessary to supplement the diet by the administration of vitamins as such. The recom-

nded da[illegible] ional
search C [illegible] 00 to
) units; [illegible] C, 75
. A "pill" containing approximately these quantities will cost the patient
m 5¢ to 7¢ (Multicebrin of Lilly, Squibb's Special Formula, Dayamin of

TABLE 11 —FOODS AS SOURCES OF DIETARY ESSENTIALS*

A	Thiamine	Niacin	Riboflavin	C
ry Products: ggs, Liver,				
etables: reen, Yellow	Cereals, Meats	Meats	Milk	Citrus Fruits, Vegetables,
reens	Pork	Liver	Liver	Grapefruit
arrots	Beef	Brewers' yeast	Brewers' yeast	Oranges
iver	Veal			Strawberries
quash	Ham	Pork	Milk	Cantaloupe
weet potato	Brewers' yeast	Bran	Prunes	Cabbage
ggs	Whole wheat bread	Salmon	Fish	Turnips
ilk		Poultry	Beef	Potatoes
heese	Dried beans	Beef	Beans	Tomatoes
	Peas	Peanuts	Eggs	
	Enriched bread		Pork	
	Oatmeal		Peas	

Food and Nutrition Committee of American Medical Association and Food and Nutrition
ard of National Research Council

bott); the full daily allowance except for the fact that the vitamin C content
nly half that recommended, can be obtained in a pill costing about 3¢ (Uni-
os of Upjohn); precisely one-half the quantities of all the vitamins can be
tained in a pill costing 2¢ (the Hexavitamin tablet of Merrill and other
nufacturers).

RICKETS

(Including Osteomalacia and Renal Rickets)

Rickets is a disease of infants that is characterized by a diminution in the
rganic phosphorus of the blood—or, in those cases in which there is an
sociated tetany, low calcium but approximately normal phosphorus—and a
ulty calcification of the newly laid down bone tissue. It is encountered most
quently between the ages of six and eighteen months, its victims being for
e most part well-nourished and rapidly growing children. The seasonal
[illegible]

dustrial cities of the north temperate zone but it does occur also in subtropi-
[illegible] the poverty-stricken class in whom dietary deficien-
e of plenty
symptoms:
ity; sweat-
he rachitic

"rosary," and enlargement of the epiphyses at the wrist; an abnormally open fontanel, coupled with a tendency for areas of softening to develop below the occipitoparietal suture. Squareness of the head, deformities of the chest (pigeon-breast or funnel thorax), knock knees or bowlegs, and curvature of the spine; any or all of these may be present. There is often "pot-belly" and usually some muscular weakness, the blood is deficient in inorganic phosphorus, which may

fed, though the latter are by no means infrequently attacked; prematurely born infants almost invariably become rachitic. It is felt by many pediatricians that the number of demonstrable cases of rickets, *i e.*, those showing some of the symptoms listed above, is not an accurate index of the prevalence of the disease, for it would seem possible, by careful examination, to elicit one or more signs of its presence in practically all rapidly growing infants; indeed, Eliot has even suggested that this state of affairs might be physiologic. It is felt at present that rickets is caused by deficiency in vitamin D (with associated calcium-phosphorus imbalance), in some other factor not yet determined, and by insufficient exposure to sunlight during the dark months. The prognosis in rickets *per se* is very good; even very pronounced deformities

defect is deformed pelvis in the female

Osteomalacia, which occurs almost exclusively in women in the child-bearing age, is generally conceded to be rickets in adults who are brought to the verge of calcium starvation by pregnancy, lactation, perhaps menstruation, and

acidosis resulting from tubular without glomerular insufficiency. The therapy of osteomalacia requires no separate consideration from that of rickets.

In the most u
"renal rickets"
evidences of ra
features of the malady are dwarfism, persistent renal insufficiency due to chronic nephritis, double hydro-nephrosis, or congenital cystic kidney, sexual infantilism if puberty is reached, hyperphosphatemia, and death from azotemia.

description of the disease was that of Francis Glisson, in 1650, Whistler having been the first to employ the English word rickets in 1645 In 1908, Finlay produced the disease experimentally for the first time by the use of a deficient diet.

PREVENTION AND TREATMENT

Cod Liver Oil.—Clinicians have used the oil empirically for a long time with excellent results in both the cure and prevention of rickets—unless we wish to

phosphorus metabolism and particularly *in the prevention of rickets*, and vitamin A The antirachitic properties of the oil reside solely in the vitamin D and are not raised by ultraviolet irradiation. The administration of the oil to mothers very much lessens the incidence of rickets in breast-fed infants.

The standard of potency per gram of cod liver oil in the U.S.P. is not less than 850 of the new vitamin A units and not less than 85 of the new vitamin D units, these units being practically identical with "International Units," and the recommended U.S.P. dose of such an oil for infants is 2 teaspoonfuls (8 cc.) daily. As a matter of fact, most Council-accepted (1947) *oils exceed in content the vitamin D standard*—the important item in rickets —and therefore in selected cases their dosage can probably be somewhat *lowered with safety. The usual procedure nowadays is to begin the administration* with 1/2 teaspoonful of the oil when growth begins to accelerate— within two weeks of birth or at least before the end of the first month— and to increase dosage rapidly so that within a week 1 teaspoonful is being taken and in two weeks more the full dose of 2 teaspoonfuls is reached; this full dose is to be continued at least up to two years of age. Average dosage is usually somewhat augmented in the case of premature infants and in unusually rapid-growing infants; in Negro and Italian infants, with their marked predisposition to rickets, double doses should be reached if well tolerated, otherwise the oil should be fortified with viosterol. The *only disadvantage* of cod liver oil is its objectionable taste and odor. It is considered advisable *to continue administering it through the summer even though* there is adequate exposure to the sun, because once stopped it may be impossible to get it accepted again.

Rancid oil is a poor source of vitamin A, it is disagreeable in taste (*more* disagreeal
ances in
Obtain a
(c) Keep mouth of bottle free from dried residue. (d) Obtain only a
supply at one time.

The flavoring of *cod liver oil, as is attempted in some of* the Council-accepted brands, does not disturb its activity. Any of the Council-accepted preparations *put up with malt extract may also* be used satisfactorily.

Cod Liver Oil Concentrate.—Several of these preparations are Council-accepted (1947) as equivalent to cod liver oil. They are marketed as oils or in tablet form. Dosage varies with the amount of concentration and is therefore that stated on the package.

Substitute Fish Oils.—The advantage claimed for *burbot, halibut* and percomorph liver oils is that while fishy in taste they do not have the rancid taste and odor of cod liver oil. The dosage here stated is that of N.N.R (1947). *Burbot Liver Oil*· 40 drops daily, or as prescribed. *Halibut Liver Oil· for infants, 6 to 10 drops*; premature and *rapidly growing infants*, 15 drops; severe deficiencies, 20 drops or more. *Percomorph Liver Oil* normal

infants, 10 drops daily; curative and in severe conditions, to 20 drops daily. There is also available a *Shark Liver Oil*, the dose of which is one capsule, or about 8 minims, daily. The burbot and halibut liver oils are also available in soft capsules.

Viosterol and Drisdol (Calciferol).—These agents, prepared by the ir- [illegible]

[illegible] is considered bad practice as some of the oil may be lost on the sides of the bottle. Accepted dosage of viosterol in oil is. average infants, 5 drops daily (standard dropper in package); premature and rapid-growing infants, 15 drops; daily curative dose, 15 to 20 drops; severe cases and adults, more [illegible]

[illegible] ministered in water, gruel, etc., 4 drops daily for the average infant and up to 15 drops daily for the premature and rapidly growing infant; daily curative dosage, 15 to 20 drops. Drisdol is also available in capsules.

The fear, earlier entertained, of inducing a state of toxic hypercalcemia by use of doses of these irradiated ergosterols much larger than the above, was probably unfounded since there are available many records of such high dosage administration without untoward effects. Tumulty and Howard (1942), to be sure, reported two cases in which the administration of repeated large doses of viosterol was associated with a prolonged hypercalcemia and persistent impairment of renal function, but it would seem that these cases may possibly be discounted since the patients were both young vigorous men immobilized in casts, a state of affairs which it is recognized in itself may produce hypercalcemia with resultant renal damage in young active individuals. However, it should be noted that in speaking of the relative freedom from toxic reactions accompanying the use of high dosage I am referring to single administrations of this high dosage or at least such administrations at long intervals in the manner presently to be described; Covey and Whitlock (1946) have recently reemphasized on the basis of their own experience what has long been known, namely, that the taking of excessively high dosage *daily* is a dangerous thing. The figure set by them that should not be exceeded daily is 150,000 units of vitamin D (the daily curative 20-drop dose of drisdol, see above, is 5000 units) Vollmer (1940) reported the successful use of single massive doses of viosterol in oil and ether, given intramuscularly, his injection mixture containing 600,000 units of vitamin D, 0 6 cc. of peanut oil and 0.4 cc. of ether. Krestin (1945) reported the successful prevention of rickets in 90 of 93 infants under two years who were given a single dose of 300,000 units of vitamin D_2 and then observed for a six-month period, the agent being given in the form of 7.5 mg. of calciferol dissolved in 1 cc. of oil and administered from a spoon after a milk feeding. Rambar *et al.* (1943) reported that the single massive oral dose of an electrically activated vaporized ergosterol (ertron), containing 600,000 U.S.P. units of vitamin D, was effective in preventing rickets in a group of [illegible]

Woll (1944), using the same preparation, gave 50,000 units at one month

of age, 50,000 units at two months, and 600,000 units at three months, administering the 50,000 unit doses in liquid form in the formula and the 600,000 unit dose in powder form in cereal. Two of his twenty-one infants showed slight roentgenographic rachitic changes one month after the second dose of 50,000 units, but after the 600,000 units were administered the processes were found to be healed four months and five days later; the remaining nineteen infants showed no rachitic changes during the total observation period of from four to nine months.

Bauer and Freyberg (1946) said that the most frequent symptoms of vitamin D toxicity are anorexia, nausea, vomiting, diarrhea, sometimes bloody stools, polyuria, muscular weakness, lassitude and headache.

Cod Liver Oil with Viosterol.—In this preparation we have oil fortified with viosterol to obtain four and one-half times as much vitamin D effect as can be obtained from the oil alone in usually tolerated doses. N.N.R. (1947) dosage: infants and young children, 2.5 to 3.3 cc. daily; adults and in severe cases, up to 7 cc. or more—this ridiculous fractional cc. dosage may be translated for practical men into approximately 1/2 to 1 teaspoonful daily or 2 teaspoonfuls or more in severe cases.

Halibut Liver Oil with Viosterol.—This preparation is said to be less disagreeable than cod liver oil with viosterol and the same vitamin D effect may be obtained with smaller dosage. N.N.R. (1947) dosage: infants, 8 to 10 drops daily; premature and rapidly growing infants, 15 drops; older children, 15 to 20 drops; adults, especially nursing and expectant mothers, 20 drops or more. Available also in soft capsules.

Antirachitic Milk.—The Committee on Foods of the American Medical Association has had before it for some years the perplexing problem of the vitamin D fortification of milk for use in the prevention of rickets. A few years ago, however, Dr. Philip C. Jeans, of Iowa City, undertook a study of the subject for the guidance of the Committee, and as his excellent review, published in 1936, is still the most authoritative available, I shall here set down what I make out to be his conclusions on the various type of product dealt with.

Fresh Milk Containing Cod Liver Oil Concentrate.—When such milk contains 400 new U.S.P. units to the quart, and is fed in customary amounts to full-

h milk, contain-
it may permit a
n. If it contains
400 units it seems entirely adequate.

Irradiated Milk.—The results with irradiated evaporated milk agree with those of irradiated fresh milk. Such milk will prevent rickets in most full-term

preven-
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een
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ized at 430 units per quart.

I think there should be appended to the above the statement kindly supplied
to wit, that although he feels
ection in the great majority
of cases of full-term infants, he
it wise to supplement with

cient in the case of premature infants in whom it is essential to supplement with vitamin D in some form during the first year. He feels that in these premature infants perhaps the best way to give vitamin D is in single massive

used

Phosphorus.—The administration of phosphorus has no legitimate place in either the prophylaxis or therapy of rickets, since the fault lies almost certainly in a failure of the calcifying mechanism rather than in faulty absorption of the bone salts.

Light Therapy.—Rickets may be both prevented and cured when infants are exposed in the light of a good type of ultraviolet-ray producing apparatus when properly used, these rays like those of natural sunlight converting the provitamin in the skin, 7-dehydrocholesterol, into vitamin D, the latter being then absorbed into the blood stream. It would be out of place to attempt a

age of rickets was nearly as high among the children of sunny San Diego, California, as among those of cloudy Portland, Oregon; they therefore concluded that under modern living conditions abundant sunshine does not pro-

everywhere as practically nonantirachitic.

Treatment of Refractory Rickets.—These cases are usually encountered in children beyond infancy. There is nothing to do but push on to enormous

three times daily during three years, the patient being eleven and one-half years old when first seen, increased the effectiveness of the vitamin D given

is of no avail in hyperparathyroidism.

SCURVY

Scurvy is a disease caused by deficiency of fresh vegetables and fresh fruits in the diet. In infants it is most frequent between the fifth and fifteenth months of life, being quite rare after the twentieth month. In adults it occurs invariably when there has been complete deprivation for as much as six months of foods containing vitamin C, now identified as ascorbic (cevitamic) acid The

a pitiable object; the body becomes edematous, dyspnea and pain are quite

portance of vitamin C deficiency in producing cardiac hypertrophy and insufficiency. In infants the symptoms are: pallor; arrest of growth and loss of weight; poor appetite; livid, swollen gums that bleed easily; and pain. This pain is manifested by a worried expression, a whimpering cry, and eversion of the thighs flexed on the abdomen. The most tender point is at the lower end of the femur. The pain in both infants and adults is caused by subperiosteal hemorrhages; in the former, in addition, there may be separation of the epiphyses and even fractures In both infants and adults marked anemia is generally present. It is thought usually to be of the hypochromic-microcytic (iron-deficiency) type, but in all of the eleven patients, severely scorbutic, of Vilter *et al.* (1946) it was normochromic and normocytic or slightly macrocytic; in Gottlieb's (1945) four severe cases it was hyperchromic-macrocytic. In two of three patients in whom bone marrow biopsies were performed, Israels (1943) found evidences of a depression of erythropoiesis rather than a failure of maturation at any particular stage. A number of cases of intracranial hemorrhage have been reported Scott (1936) recorded a case of atypical scurvy in a girl of fourteen years whose only presenting symptom was a spontaneous subaponeurotic hematoma that gave her the appearance of having ordinary hydrocephalus.

Scurvy was unmistakably described by Jacques de Vitry in the forces of the Crusaders who were besieging Damietta in 1218, but earlier reference to the disease has not been discovered, unless a doubtful passage in Hippocrates be accepted. Always, at least since the Middle Ages, it has ravaged armies and beleaguered cities, and when long sea voyages began to be made it quickly struck at the crews of vessels; Hofmeyr (1941) has interestingly recounted how, in 1652, the Dutch made their first settlement at the Cape of Good Hope for the express purpose of supplying fresh fruits and vegetables to the scurvy-ridden crews of ships engaged in passage between Europe and the Far East. In passing, it may be of interest to note that the lime juice with which the British Navy rid itself of scurvy after 1795, and incidentally won for its crews the undying soubriquet of "limeys," was not lime juice at all but only the juice of the humble and far less exotic lemon. Nowadays expeditions to far-off places are protected by nothing more romantic than crystals of ascorbic acid. Scurvy caused severe losses in certain areas during War I, being especially destructive among the British troops who were

besieged at Kut-el-Amara. Then, during the interim of partial and precarious world peace, the disease seemed to be endemic among adults in northern Russia and China and certain parts of the tropics, in the latter region occurring principally, according to Manson-Bahr (1946), among coolie gangs recruited for labor purposes and placed on a dietary of dried cereals and preserved foods. Doubtless, however, as shown by the studies of McDevitt *et al.* (1944) in Newfoundland, severe grades of vitamin C deficiency might have been found in many regions for the looking. With the planet ravaged once more during War II, scurvy took a high toll again, though Musselman (1945) said that for some reason in the Cabanatuan prison camp where so many deficiency diseases were rife, scurvy never constituted a serious problem, though he felt that probably subclinical scurvy played an important role in the long delay in the healing of wounds that was such an embarrassing surgical problem in the camp Here in the United States, and elsewhere in lands not recently under the plunderer's heel, scurvy has for a long time existed principally as a problem in infant feeding, though during the depression years sporadic cases were reported among adults upon whom the disjointed times forced semistarvation in the midst of plenty. Meulengracht several years ago drew attention to the fact that scurvy is also not to be overlooked in unmarried individuals who live alone and prepare in their own rooms a diet that is nearly always deficient in the items of meat, fruits and

have also

special die

ances or taken as a matter of choice by eccentric individuals The fine study of Lund and Crandon (1941) also indicated the advisability of investigating the dietary history of patients coming to major surgery since marked vitamin C deficiency delays or even prevents wound healing.

The recent study of Holland *et al.* (1947) confirmed the almost universally held view that the vitamin C saturation test provides an excellent index of the patient's vitamin C status.

THERAPY AND PREVENTION

Dietetic Treatment.—Scurvy may be easily cured simply and solely by the addition to the diet of a sufficient amount of the antiscorbutic factor. Unpasteurized milk and raw meat contain this factor, but either must be taken in very large quantities in order to suffice; fresh vegetables, especially

juice are hardly effective at all These fruit juices, *i.e.*, two or three oranges or lemons daily (or the same number of bananas), or somewhat more than equivalent quantities of the canned juices, or the liberal use of fresh vegetables not too long cooked, will very rapidly cure a case of scurvy. It is best in preparing the juices at home to use only glass or china receptacles as iron and copper rapidly destroy the vitamin; after more than two days of refrigerator storage fresh juice depreciates considerably even if covered Stale vegetables are of little value, and fruits and vegetables preserved by artificial drying are practically worthless. By new processes it has now become possible to can fruits and vegetables without destroying completely the antiscorbutic factor; the quick freezing process also preserves some of

the vitamin; the commercial vogue for quick ripening by ethylene is apparently not harmful. In many instances past and present ingenious persons and even large populations have saved themselves from scurvy by drinking copiously of a tea brewed from pine needles.

The disease is prevented by the same measures that suffice for cure. In the case of infants not being nursed by mothers *who are taking liberal amounts of antiscorbutic foods, since both the fetus and the suckling infant drain the mother's supply,* the vitamin factor must be artifically supplied after the first two weeks of life.

Ascorbic (Cevitamic) Acid.—In 1928, Szent-Györgyi isolated hexuronic acid from the suprarenal gland and concluded that it is identical with the reducing substance in active vitamin C concentrates. The first definite identification of the substance as vitamin C was made by Waugh and King in 1931, published in 1932. It is currently prepared from adrenal glands, and from citrus fruits, cabbage, peppers, and other plant sources, and is also produced synthetically. Commercially it is available in the form of crystals, in capsules, tablets and ampules of solution. The study of Wilson and Lubschez (1946) showed that the daily allowance of 50 to 75 mg. of ascorbic acid recommended for children by the National Research Council is certainly not excessive, but they felt that an habitual daily intake of 200 to 600 mg. is unnecessary and inadvisable. In treating multiple vitamin deficiencies, Spies and his group in Birmingham use a basic formula containing 10 mg. of thiamine, 50 mg. of niacin, 5 mg. of riboflavin, and 75 mg. of ascorbic acid; in th
daily in a
acid may
or sterile
reaction I have seen is that of Anderson and Leake (1935): chill, fever and general discomfort in a patient given 100 mg. of the drug.

Treatment of Anemia.—This matter is discussed in the section on Anemias.

PELLAGRA

need to be somewhat elaborated upon of course
defined, is nearly always symmetrical and is usually confined to those areas of the skin that are exposed to light, *i.e.*, the face and neck, the backs of the hands and the lower parts of the forearms, the feet and the lower legs. Very
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panying abdominal pain or of the stool except
and watery (vaginitis, urethritis, and endocervicitis are also frequently present). More or less severe stomatitis, glossitis, gingivitis, pharyngitis, gastritis, achylia gastrica and enteritis are prominent features in most cases Musselman (1946) said that in the Japanese prison camps in the Philippines the tongue

often became a swollen, raw beefy mass that interfered with speech and chew-

the disease in an endemic area the mortality is quite low even without treatment.

In recent years a few cases of pellagra have been reported in association with the symptoms of Addison's disease Seale Harris (1941) said that heart complications occur relatively infrequently However, Rachmilewitz and Braun (1944) reported two cases in which the electrocardiographic changes were reversed through the administration of niacin (nicotinic acid) Moore *et al.* (1944) have called attention to the macrocytic anemias that occur in some patients with pellagra

The first published account of pellagra was that of Casal, in Spain, in 1735. Shortly thereafter it was recognized as a widespread malady in northern Italy, where it was exhaustively studied by Strombio in 1786–1789 In the present post-War II days the incidence is probably higher all over the Continent than it has ever been during the modern era, but even in "normal" times it has been quite prevalent in southern Europe and the Balkan States, Poland, Asia Minor, Transcaucasia, India, Japan, China, Korea, Manchukuo, Eygpt, the Sudan, Algeria, Tunis, the Red Sea coast and many regions throughout Central, West and South Africa, the West Indies, Central America and the southern United States. Doubtless the disease could have been found elsewhere for the

the necessary antipellagric vitamins through one or a combination of several of the following factors· "finickiness" in eating, addiction to dietary faddism, chronic alcoholic addiction, a prolonged illness with poor alimentation or a relatively short illness with high fever, gastro-intestinal pathology interfering

diet. Benesch (1945) has developed the interesting hypothesis that in the normal cecum an equilibrium is struck between organisms that produce and those that destroy niacin and that an upset in this equilibrium may play a part in the causation of the deficiency syndrome.

Pellagra occurs in persons of all ages; blacks and whites, and probably all other races, are equally stricken. In the endemic areas of the South cases make their appearance principally in the spring and persist until the middle of the summer. Musselman (1946) said that in the notorious Cabanatuan prison, in which the remnant of the Bataan forces were incarcerated by the Japanese during War II, the clinical signs of pellagra required four to eight months to establish themselves but that, once established, the course of the disease was relatively rapid. The disease "kwashiorkor," encountered by Williams (1933) in Accra on the Gold Coast, was believed by Stannus (1936) to be merely pellagra in children, but Trowell (1946) is now willing to subscribe to the belief, consistently held by Williams it seems, that this is not pellagra but a new

though others had recorded success with it, and also suggesting that kwashiorkor is perhaps not a nutritional disease at all. Hare (1947) described cases of this malady seen in India.

THERAPY

through demonstration of the following things: (a) that inadequate diets were uniformly eaten by human beings who contracted pellagra: (b) that such diets ... animals caused a similar disease in them: (c) that liberal

l diseases; (d)

feeding them

nals And the

central fact in the above summary of Goldberger s findings is still true, *i.e.*, a

... the cure of pellagra.

vitamin

without

a change in dietary, it is nevertheless the burden of the testimony of the leaders in this field of study that a return to an adequate dietary is the thing to be chiefly desired not only for permanent cure of pellagra itself but also because the diet of pellagrins is one that practically always causes other deficiencies as well Handler's (1947) fine article is commended to the reader who would ... complexities of pellagra. The problem

involving questions of food

other things that determine

o learn from Kooser and

Blankenhorn's (1941) study that even in a community in which economic betterment had not taken place a long campaign of education in the health-sparing value of foods could be highly successful They compared two adjacent neighborhoods with similar economic status in the mountain counties of Kentucky. The one that got rid of pellagra had learned to have gardens, cows and chickens, and the one that still suffered pellagra had only insignificant gardens and the local grocery stores as sources of food. There was not much

pellagra is undertaken the essentials of the dietary to be enforced may be condensed from the studies of Spies and his associates into the following: a

obtain for the pellagrin or to persuade him to eat. De Kleine (1942) says that of the various factors contributing to the marked reduction in pellagra mortality in the South in recent years, none has been more important than dried brewers' yeast, though Remington (1944) felt it not easy statistically to substantiate this statement. The amount usually administered in a full-blown case, if the patient can be got to take it, is 75 to 100 gm. daily. One manufacturer makes the following suggestions for palatably mixing one level teaspoonful (2.5 gm.) of this powder: (1) shake in cocktail shaker with 4 ounces of milk (with or without 1 level teaspoonful of sugar and cocoa); (2) stir with fork into 3/4 ounce of catsup or chili sauce—optional, add a few drops of lemon juice, (3) stir with fork into 3 ounces of soup (preferably thick soup such as bean, pea, oxtail, beef, etc.), (4) spread on bread with two to three times the amount of peanut butter; (5) add 1 level *tablespoonful* (and a little extra salt) to two cups of meat stock gravy. Several years ago Spies described his very satisfactory use of a peanut butter-yeast mixture: 75 per cent of peanut butter and 25 per cent of a special "C-50" strain of relatively palatable yeast supplied to him by the research department of one of the large breweries. The patients ate this mixture *ad libitum* at two of the daily meals, consuming an average of 60 to 75 gm., in some instances as much as 160 gm., per day. This mixture contains niacin (nicotinic acid), riboflavin and thiamine, and per unit weight as much carbohydrate as potatoes, more protein than steak, and one-half as much fat as butter. This yeasted peanut butter mixture can be bought as "honey peanut butter" from the Andrus-Scofield Company, Columbus, Ohio, and is locally procurable in many places. N.N.R. (1947) contains brewers' yeast powder, the same fortified with niacin and riboflavin, brewers' yeast tablets in 5, 6 and 7½ grain (0.3, 0.4 and 0.5 gm.) sizes, the same fortified with niacin and riboflavin, and also a liquid extract and a syrup containing vitamin B complex.

According to Musselman (1945), in the Cabanatuan prison camp during War II, wild yeast cells from the air were cultured in a thin medium prepared from such materials as could be spared and he said that this preparation was used with good effect in even severe cases of pellagra.

The Use of Vitamins in Therapy.—When dietary correction cannot be made, or when there is reason to believe that some degree of subclassical pellagra exists in spite of the taking of an ordinarily adequate diet, or when the patient is very ill and it is necessary to accomplish arrest and cure of the condition as quickly as possible, under these conditions resort should be had to employment of vitamins in pure form. Since the showing, by Elvehjem and his associates, in 1937, that niacin (nicotinic acid) is effective in curing experimental canine pellagra, and the dramatic improvement in

many of the symptoms in the human form of the disease, first reported by Fouts *et al.* in the same year and subsequently by many observers throughout the world, this vitamin has been accepted as the specific curative agent in pellagra. The *improvement effected by its use is undoubted and often* dramatic, but such leaders in the clinical phases of this work as Spies and Sydenstricker find that all symptoms are not always caused to disappear in all cases; that indeed thiamine (vitamin B_1) therapy is necessary to clear the neuropathic part of the picture; and that *sometimes riboflavin must* also be used and in an occasional case even pyridoxine (vitamin B_6). In short, pellagra is a disease in which the outstanding deficiency is in niacin, but in which the other elements of the B_2 complex *may also be deficient, and furthermore* a deficiency in B_1 (thiamine) is often associated with if not integrally a part of the pellagrous picture. Musselman (1946) said that in the Cabanatuan camp in some cases severe pellagra was only partially controlled with as much as 500 mg. of nicotinic acid a day, it being observed that the patients in this group were frequently of a blonde or sandy complexion; but he also said that he and his associates were amazed at the degree of protection afforded by 1 capsule of multivitamins per day after this medication became available through the American Red Cross.

Spies and his group at the Nutrition Clinic at the Hillman Hospital in Birmingham, Alabama, in treating the vitamin deficiencies use a basic formula *containing 10 mg of thiamine, 50 mg of niacin, 5 mg of riboflavin and 75*

if not more so, than the former

NICOTINIC ACID DEFICIENCY ENCEPHALOPATHY

Jolliffe *et al.*, in 1940, reported an interesting series of 150 cases of an encephalopathic syndrome characterized by clouding of consciousness, cogwheel rigidities of the extremities and uncontrollable grasping and sucking ... ssociation *with manifestations* ... and scurvy. Sydenstricker ... se findings, each in a smaller *series of patients*, and it seems to me that the cases described by Graves (1947) among prisoners of war in Singapore could probably be made to fit into this picture. Patients with this malady treated by hydration alone or plus thiamine almost invariably die; patients treated by hydration plus ...

permissible to look upon the pellagra syndrome as ... deficiency of niacin of sufficient duration to produce *the structural* changes recognizable in the clinical picture of pellagra, but that in the encephalopathy *under discussion practically* complete deficiency develops so rapidly that there is no time for the development of the pellagrous picture.

THERAPY

Sydenstricker (1943) says that very large amounts of niacin (nicotinic acid) are required during the first few days of treatment He customarily gives 100 mg of niacin or 30 mg of the amide every hour for ten hours during the first two days, continuing this dosage longer if necessary. Where co-operation is not obtainable the vitamins must be added to intravenous or

niacin can be reduced to 500 mg. and of the amide to 150 mg. Later the oral administration of 25 mg. of niacin three times daily usually suffices for maintenance Gottlieb (1944) feels that half Sydenstricker's dosage would be adequate in most cases though agreeing that when the full picture is developed the full dosage should be given Both he and Sydenstricker feel that thiamine should be given as well as niacin Sydenstricker uses the empirical rule of giving one-tenth as much thiamine as niacin, he says that this is probably wasteful but seems effective He also favors the addition of dried brewers' yeast, 15 to 30 gm daily, to the diet regardless of the amounts of the crystalline vitamins that have been given.

ARIBOFLAVINOSIS

(*Including the Oro-Genital Syndrome*)

eighteen patients to whom they gave a special diet low in riboflavin content

South it occurs more frequently than any other deficiency syndrome; Sydenstricker *et al.* (1940) say it is possibly the most prevalent, without any age limitations, of all the apparently uncomplicated avitaminoses—Goldsmith's

present understanding of Cayer's (1947) position is that he feels that invasions of the cornea and cheilosis are too often looked upon as specific indications of ariboflavinosis when they may in fact be expressions of deficiencies in other essential nutrients. The disease has been reported in England and appears to be widespread in India, China, Malaya and Africa.

Many of the symptoms of which the victims of this disease complain are characteristic of all the vitamin deficiencies, namely, weakness and easy fati-

gability, anorexia, gastric discomfort and insomnia, but the diagnostic signs of specific ariboflavinosis are the reddened macerated areas at the angles of the mouth known as "cheilosis," scaly-greasy lesions in the nasolabial folds and on the alae nasi and ears, a specific glossitis in which the tongue is roughened and fissured and purplish-red or magenta in color instead of scarlet as in nicotinic acid deficiency, a tendency for the appearance of a "shark-skin" type of eruption and seborrhea that may be very extensive, pruritus ani and vulvae, and finally ocular symptoms characterized by circumcorneal injection and corneal vascularization, lacrimation, burning of the eyes, mydriasis and disturbances of accommodation, and failure of vision especially in dim light. In one third of the cases of Sydenstricker *et al.* (1941) there were changes in the appearance of the iris, and this group of investigators believe that at least one of the varieties of keratitis, that known as rosacea keratitis, is really the corneal vascularization of riboflavin deficiency. In India it has become customary to recognize an "oro-genital" syndrome consisting of angular stomatitis, glossitis and scrotal

[illegible]

United States as well as elsewhere the classical symptoms are not always presented as a result of deficiency in riboflavin solely. It is of interest to note that Musselman (1946) reported the occurrence of scrotal dermatitis in cases of "pellagra" occurring in the Cabanatuan prison camp during War II. (See Pellagra.)

[illegible]

tion in a medium of low hydrogen ion content Stevenson (1942) reported a [illegible] flavinosis appearing on the thirteenth day of life in a

[illegible]

which proved unresponsive to riboflavin therapy; however, none of these patients had ocular or seborrhea-like lesions, and further intensified study revealed that the labial and lingual disturbances resulted from ill-fitting dentures.

THERAPY

Sebrell *et al.* (1941) presented data indicating that the daily intake of 3 mg. of [illegible]

basic vitamin ration, described in Pellagra (*q.v.*). The drug is [illegible] tablets, capsules and ampules for parenteral *administration*. Spies *et al.* (1945) described as remarkable the degree of improvement in the ocular symptoms in patients treated for brief periods with intravenous injections of 10 to 15 mg. daily. In India, Mitra (1943) effected cure in from twelve to seventeen days in sixteen of eighteen patients with the oro-genital syndrome whom he gave 5 mg. daily by mouth; the two resistant cases cleared within five days when changed to 3 mg of riboflavin plus 100 mg. of nicotinic acid (niacin). Spies and his group found their cases responding to either riboflavin, brewers' yeast, or liver extract, and both he and Butler stress the importance of getting these patients

onto a diet that will supply plenty of the B complex: liver, lean meat, milk, eggs, whole wheat or enriched cereals, and the highly colored vegetables.

No toxic reactions following riboflavin administration have been reported in man.

BERIBERI

In recent years great strides have been made in our understanding of this disease which is now known to be due to thiamine (vitamin B_1) deficiency. It seems to me that, from the practical standpoint, the entity can be divided into [illegible]

with areas of paresthesia and superficial anesthesia, and with diminution or loss of the deep reflexes. Diminution in vision often appears. The edema [illegible]

sonnel afflicted with the disease developed motor paralysis whereas over 75 per cent had predominantly sensory disturbances or painful feet; this "painful feet" syndrome was described by a number of observers recording the occurrences in widely scattered Japanese prisoner of war camps. An interesting lesion he also described as having been commonly seen in patients with peripheral neuritis was said to have resembled erythema nodosum; it was called beriberi spots, though the medical group in the camp could not be certain because of lack of facilities that it was truly due to thiamine deficiency. The heart, especially the right side, becomes greatly enlarged, and the patient dies [illegible]

[illegible] ft and [illegible] na and [illegible] . "dry" type, the edematous phenomena predominating over the nervous system [illegible]

[illegible] disintegrative changes in the brain cells, though mental symptoms to [illegible]

the more profound mental changes do not respond completely and at once to thiamine. However, de Wardener and Lennox (1947) concluded from their study of fifty-two cases of this syndrome seen in a Japanese prisoner of war camp during War II that the name cerebral beriberi may be aptly applied

to this syndrome since early treatment with thiamine injections alone rapidly and completely cured cases.

It is said that references to classical beriberi are contained in very ancient Chinese and Japanese manuscripts, but Wilder (1943), after studying translations of the early literature, is doubtful of the authenticity of these early cases. At present the disease is endemic in Japan, China, Indo-China, the Straits Settlements, the Netherlands Indies, the Philippines, Newfoundland, Labrador, and Iceland, and here and there in India ("beriberi" in Singhalese, the native language of Ceylon, means "I cannot"), the West Indies, South America and some parts of "native" Africa and Australia. To what absolute extent beriberi developed among the populations enslaved during War II is not as yet a matter of record, but Hibbs (1946) stated that among the prisoners of war after the surrender of Bataan and Corregidor everyone had some form of the disease at one time or another and that it was directly responsible for more deaths in the prison camps than any other vitamin deficiency.

It was Takaki who first proved by his dietary readjustment in the Japanese Navy, in 1883, that beriberi is caused by a food deficiency. He held that it was protein that was lacking in the diet, but the observation of Eijkman, in 1896, that a polished rice diet always caused the disease, and the subsequent researches of many investigators, have shown that the missing substance is vitamin B_1, which has been isolated and synthesized as thiamine. This substance is concentrated in the outer layers of the cereals, especially rice, that are used for food by the native populations of large areas in the tropical and subtropical regions all around the globe; furthermore, it is removed by modern milling processes, and therefore peoples who subsist during certain portions of the year almost exclusively upon this polished rice suffer from the deprivation of vitamin B_1; that is to say, they develop beriberi It is a mistaken idea, however, that rice eating alone will cause the disease, for it follows also upon a prolonged period of the monotonous eating of other completely milled cereals, such as wheat or corn, or such a diet as white bread, molasses, sugar and fats. Likewise, too exclusive reliance upon canned food invites the disease. Occasional outbreaks of classical beriberi occur in faultil [illegible] but the number of cases is usually not large befor [illegible] However, in 1903, Young, and later [illegible] ntion to the fact that the "maladie [illegible] iana is beriberi. We are now aware also that the disease occurs sporadically with fairly high frequency throughout the whole United States and needs only to be looked for to be found. In five years at the Cincinnati General Hospital, Blankenhorn *et al.* (1946) were able to recognize beriberi heart disease in twelve patients, an incidence of 0.1 per cent of all medical admissions. The victims in these instances are individuals who, for one of the following reasons, ingest a diet deficient in thiamine. chronic alcoholics, who not only substitute liquor for much of their food but also require thiamine to metabolize the alcohol, and who are also likely to have gastro-intestinal disturbances that interfere with absorption, the pregnant woman, whose metabolic requirement (and hence thiamine requirement) is increased by gestation, but who may nevertheless severely restrict her diet because of nausea and vomiting; patients with any type of gastro-intestinal disturbance limiting ingestion, retention, or absorption of food, the use of severe elimination diets

because of food sensitivities; febrile diseases in which increased metabolic requirement is accompanied by anorexia; possibly thyrotoxicosis in some instances; cirrhosis and other liver derangements that seem to inhibit utilization of thiamine; perhaps severe parenchymal damage to any internal organ may raise thiamine requirement; maintenance of a patient exclusively on intravenously or rectally administered dextrose solution; and probably in a few instances there are individuals whose thiamine requirement is higher than can be obtained from a normal dietary. Waring (1929) recorded the occurrence of beriberi in a two months' old infant and Rascoff (1942) in one of four months; in Van Gelder and Darby's (1944) case the infant was born with severe, almost fatal manifestations of beriberi. Rascoff pointed out [illegible]

The patients of Williams *et al.* (1941), who were carefully selected and cooperative throughout the course of the thiamine-deprivation studies, manifested several or all of the following signs or symptoms. capriciousness of appetite sometimes going to the point of intolerance for food; low blood pressure and faint cardiac sounds, marked sinus arrhythmia; palpitation and a pulse rate exceeding normal limits on moderate exertion; giddiness [illegible]

and loss of manual dexterity, headache, backache, dysmenorrhea, soreness of muscles, gastric distress after meals, sleeplessness, tenseness, paresthesia, intolerance to noise and increased sensitivity to painful stimuli. Studies similar to those of Williams were performed also by Jolliffe *et al.* (1939), with similar findings. And the amazing and important thing about both these investigations is that the diets employed were of about the quality that a shockingly high proportion of our populace is accustomed to employ routinely. The inescapable conclusion—a thesis already elaborated by Jolliffe several years ago—is that the incidence of subclassical beriberi must be high in our land.

Infantile beriberi has long been recognized as a dreadful scourge in the Far East for the incidence is high and the death rate apparently over 90 per cent. *It is a disease of breast-fed infants whose mothers are thiamine-deficient.* Methylglyoxal has been isolated from the milk of such women, and Fehily (1943), formerly of Hong Kong where she made a considerable study of the disease, apparently feels convinced that the death of these infants, which often occurs quite suddenly, is due to poisoning by methylglyoxal imbibed in the milk. In India, however, Krishnan *et al.* (1945) found that infantile beriberi responds well to parenterally employed thiamine.

THERAPY

Thiamine.—The use of the specifically deficient agent, thiamine hydrochloride, has of course revolutionized the treatment of beriberi, its employment effects a dramatic alteration in the patient's condition, and progress thereafter is steady and rapid to recovery. Spies and his group in Birming-

ham, in treating specific thiamine deficiency, add 10 mg. daily to their basic vitamin formula (described in Pellagra) that already contains 10 mg. In fulminating cases it is the practice of most men of large experience to give the first few doses intramuscularly, subcutaneously, or even intravenously. In some urgent cases Jolliffe and Rosenblum (1939) have used as much as 1000 mg. in the first twenty-four hours. After the patient is saturated with thiamine (the urine acquires a burnt rubber odor) dosage may be reduced to a much smaller amount, such as 5 to 10 mg. daily. As a matter of fact, I imagine increasing experience is going to show that doses larger than this are probably rarely necessary at any time. Mills (1941) mentioned a few cases of patients who developed symptoms resembling those of hyperthyroidism apparently as a result of thiamine therapy; cessation of the drug was followed by prompt disappearance of these symptoms. There have been several reports of an anaphylactic type of reaction occurring in a patient apparently sensitized by repeated injections of thiamine; the patient of Reingold and Webb (1946) died; Mitrani's (1944) patient presented an eruption after the first as well as all succeeding injections of thiamine. However, it is not entirely certain that death cannot be caused directly by the toxic action of thiamine in large doses given parenterally, for Haley and Flesher (1946) have found that anaphylaxis plays no part in thiamine toxicity as seen in rabbits. There would seem to me to be no reason to use the drug parenterally in the vast majority of instances since tablets of various sizes are available for oral use and prompt improvement is the proof of gastrointestinal absorption; in any case the performance of an intradermal test before injecting would seem the part of wisdom. Klopp *et al.* (1943) found that in many instances the administration of thiamine is followed by an unexplained transitory increase of riboflavin excretion in the urine.

Supplementary B Complex.—Wilder (1943) doubtless expressed the consensus when he said that in addition to thiamine the vitamin B compl[illegible]
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puréed, other vege
variety of meats permitted with [illegible] should be added, and [illegible]
muscle [illegible]

NUTRITIONAL EDEMA

(*Famine Edema*)

This is a beriberi-like state that was distressingly prevalent in the blockaded countries of central Europe during War I. During the present nutritional crises in Europe and in China subsequent to War II, it is certain that the incidence of [illegible]

suffering from this malady there is edema of variable grade and complaint of weariness and easy fatigability; the total protein and albumin of the blood serum are below normal, but the heart is not enlarged and polyneuritis is not a characteristic symptom This illness results from living on a diet containing insufficient protein and too much fluids and salt. Precisely how much nutrition- [illegible]

the preparation of food, it is not to be confused with this entity.

THERAPY

The chief aim is of course to restore the serum protein, which can usually be accomplished by employing the ordinary adequate diet, though oftentimes considerable coaxing and catering to whims will be required in persuading the patient to partake of a diet with normal protein content. Laycock (1944) stressed liver, meat, fish and soy bean derivatives in his cases, and found that [illegible]

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Supplementary B Complex.—Wilder (1943) doubtless expressed the consensus when he said that in addition to thiamine the vitamin B complex as a whole should be provided, he suggested the daily injection of a concentrated liver extract in 3 cc doses, or otherwise the giving of dried brewers' yeast by mouth in doses of 45 to 60 gm a day. Hibbs (1946) reported that in a selected group of prisoners of war in which the Japanese permitted an experiment to be performed it was found that beriberi peripheral neuritis responded sooner to the entire B complex than to thiamine alone According to Musselman (1945), wild yeast cells from the air were cultured in such materials as could be spared in the Cabanatuan camp and used quite successfully in the treatment of ev severe cases

Diet.—The dietary requirements for the correction and the prevention o recurrence of beriberi are the following, according to Jolliffe and Rosenblum. When the patient is extremely ill, limit the diet to milk, eggs, ground liver, puréed legumes, thin whole wheat cereals, and fruit juices, administered if necessary through a nasal catheter. Following improvement, or in less severely ill patients, whole wheat bread should be added, the legumes need not be puréed, other vegetables and raw whole fruit should be added, and a wider variety of meats permitted with substantial portions of either liver or pork muscle included in one of the meals daily. All vitamin-free foods such as unfortified white bread, pastries, alcohol, corn syrup, candy, corn starch and soft drinks should be eliminated from the diet.

NUTRITIONAL EDEMA

(*Famine Edema*)

This is a beriberi-like state that was distressingly prevalent in the blockaded countries of central Europe during War I. During the present nutritional crises in Europe and in China subsequent to War II, it is certain that the incidence of nutritional edema is extremely high although no accurate figures are as yet available. Laycock (1944) gave us a picture of this entity as he saw it in Chinese prisoners who, after a period of deliberate and systematic starvation by the Japanese in occupied China, were then released into free China. In patients suffering from this malady there is edema of variable grade and complaint of weariness and easy fatigability; the total protein and albumin of the blood

al edema there is in the world during times of relative peace, and how much of the alleged beriberi is truly this entity, is not definitely known, but presumably the incidence is very high in those regions where chronic undernutrition obtains among the masses. Isolated cases were reported in all the more advanced countries during the economic slump that preceded War II. Cases are also seen accompanying some malady in which sufficient intake or utilization of protein foods has been impossible. Epidemic dropsy, occurring principally in restricted areas in India, is now known to be due to an adulterant of mustard oil used in the preparation of food, it is not to be confused with this entity.

THERAPY

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signs of peripheral circulatory failure; in a number of such patients he found low serum sodium and chloride levels apparently as a result of loss of these elements in the stools Excessive crossness and irritability, periodically accompanied by moderate fatty diarrhea and vomiting, may be the thing that primarily brings the very young patient under medical observation (Hanes and McBryde, 1936); the adult victim also manifests evidences of nervous system involvement, such as insomnia, depression, moroseness, irritability—even apparent subacute combined degeneration of the cord has been occasionally observed (Weir and Adams, 1934; Woltman and Heck, 1937).

in a hyperchromic-macrocytic fashion, though in adults this form of reaction results from diverse injuries. Rarefaction of bone (osteoporosis) and tetany are characteristics of the disease at all ages, but stunting of growth, infantilism, fractures and bone deformities are seen more frequently in those patients whose malady began as "celiac disease" in infancy; bone pain is more often encountered in young patients also—these differences are likely due to the greater lability and vulnerability of the bone-forming mechanism in youth. Skin disturbances of various sorts are of frequent occurrence in sprue, and the abnormal pigmentation sometimes seen may closely resemble that of pellagra, perhaps even suggest Addison's disease. The van den Bergh (indirect) reaction is not increased in sprue as it is in pernicious anemia, and achlorhydria occurs no more often perhaps than in otherwise normal individuals. Cayer *et al.* (1945) found that the determination of plasma levels of vitamin A and of carotene is a useful laboratory procedure since in a thorough study of twelve cases they found the levels of vitamin A and carotene significantly lower than in normal individuals or in those having a B complex deficiency.

It is currently the accepted opinion that the symptoms of sprue result from a functional disturbance of the small intestine that interferes with absorption. No satisfactory explanation for the appearance of this functional disability has been offered, but Vedder's (1942) tentative explanation of the symptoms may be summarized as follows: interference with fat absorption causes the steatorrhea and later the diarrhea, later the absorption of glucose is impaired and its resulting fermentation gives rise to the distention and frothiness of the stool; diarrhea diminishes absorption of calcium and iron and of vitamins; the diminished absorption of vitamins sets up a vicious circle through aggravating the intestinal symptoms and causing still further lack of absorption. Stannus (1942), in a thoughtful review of the subject, presented the hypothesis that the primary failure in sprue is one of phosphorylation due to defective enzymic action, the enzymes involved probably having as the active part of the molecule coenzymes embodying some members of the vitamin B_2 complex; Maegraith was in agreement at least as far as the faulty phosphorylation of fatty acids was concerned. Leishman (1945) has very cleverly attempted to reconcile the apparent infectious with the apparent deficiency basis of sprue by reasoning that if Benesch's (1945) observation is correct, namely, that there must be maintained in the gut an equilibrium between the organisms that produce and those that destroy vitamins, then the infectious nature of sprue might merely mean that there occurs at some time a swamping of the normal synthesizing bacteria by

SPRUE

(Nontropical Sprue, Celiac Disease [Gee-Herter-Heubner Disease], Idiopathic Steatorrhea [Gee-Thaysen's Disease])

In the middle of the eighteenth century, sprue was observed and described by Hillary in the West Indies. Subsequent modern reports, by Manson in China and Van der Burg in Java, both in 1880, started us off with the fixed belief that this is exclusively a tropical disease, and obscured the two important facts that sprue had actually been described as early as 1669, by Ketelaer, occurring among Belgians in their native land, and that in the present day in ... be found. Likewise, the ... "the coeliac affection" ... nmon with sprue that it may now also profitably be considered as identical with that malady—Wilder (1944) probably expressed the consensus of students of the subject when he said that celiac disease bears the same relationship to sprue that cretinism does to adult myxedema. However, Andersen (1947) concluded as a result of her ... picture of celiac disease with ... he ... h- ... f the colon ...

been measured, since they have found some patients having a clinical picture resembling that of sprue in whom autopsy revealed obstructive changes due to pancreatic fibrosis.

Sprue, which tends to progress in a series of exacerbations, is characterized by a sore and excoriated tongue and buccal mucosa; excessive intestinal fermentation; stools that contain excessive amounts of split fat and soaps and either resemble dirty brown dishwater or are light-colored, very bulky, fetid and sometimes frothy; a very low "flat" blood sugar curve; a reduction in calcium and phosphorus in the serum; and a blood picture, regarding the formed elements, practically identical with that of pernicious anemia. The ...

normal mucosal folds, and pain produced by the rectal examination in excess of that felt by other patients. Dilatation of the colon has often been noted; the original demonstrations by Snell and Camp (1934), and Mackie et al. (1935), of characteristic roentgenologic changes in the small intestine that vary with the severity of the clinical picture and regress under specific therapy, have been confirmed Except in the terminal stages, diarrhea is not so frequent as it is exhausting In long-standing cases the victims become very cachectic and die from inanition or intercurrent disease Keele and Bound (1946), analyzing their experience in India during War II, said that suppressed or latent malaria exacerbates sprue and that eradication of the malarial infection rapidly improves the sprue syndrome Black (1946) said that fatal cases of sprue occur principally in individuals who have developed hypotension and

in the peripheral blood, the tongue is less angry looking, a few new papillae [illegible]

[illegible]

were acute and full-blown and the rest old cases that had been maintained in relatively good health for a number of months or years under adequate liver therapy, Suarez, Spies and Suarez (1947), in Puerto Rico, confirmed and extended the earlier observations of themselves and others on the efficacy of the agent. They found that the administration of small daily doses is more effective than many times as much given in a single dose, the daily oral administration of 10 mg. being adequate. They also found that a relatively small dose of folic acid accompanied by an adequate sprue diet produces better results than the administration of larger doses unaccompanied by an adequate diet. They gained the impression that 2 5 to 5 mg. daily would probably be found adequate as maintenance dosage for the majority of [illegible]

[illegible]

ment with folic acid despite the fact that no antiparasitic therapy was employed. It should be noted, however, in the enthusiasm for this new remedial agent in sprue, that Davidson *et al.* (1947), in Scotland, were unable to obtain satisfactory hematological responses in their cases, and that Comfort (1947) reported that at the Mayo Clinic their findings indicated that at least some patients do not respond in any particular as well to folic acid as to liver extract.

Diet.—Numerous dietary regimens have had their day in sprue and even now that we are treating cases "specifically" with live extract and folic acid, diet is still considered very important. A few patients, once they have recovered under liver therapy, can maintain their health by proper dieting alone (and possibly this would prove to be the case with folic acid also), but even if liver extract must be more or less continuously employed a rigid diet must nevertheless be adhered to The successful diet is one essentially high in protein, with stress upon the taking of large quantities of rare red meats, and in monosaccharides, but low in fat, starches and other polysaccharides. Barker (1943), at the Johns Hopkins Hospital, uses the diet shown in Table 12 in all patients unless the severity of their condition makes it impracticable, in which case they are given nothing but ground meat, bananas and skimmed milk until they can partake of the more liberal diet. Barker finds it often valuable to add dried brewers' yeast or rice polishings to the diet as sources of the vitamin B complex. When fresh milk is not available, dried milk powder has been used satisfactorily.

Adjustment Therapy for Celiac Disease.—In youngsters with celiac disease, May *et al.* (1942) reported the injection of 2 cc. of crude liver extract (Lilly) one day and 4 cc of parenteral vitamin B complex (Lederle) the next day, the injections being given intramuscularly into the buttocks and continued for three weeks or until clinical improvement was observed; thereafter vitamin B complex, at least one teaspoonful four times daily, was [illegible]

organisms antagonistic to them but not in themselves giving rise to pathogenic lesions; or on the other hand, he makes the point that a similar effect might well result simply from a change in the intestinal media such as might follow unaccustomed diet or altered gastric acidity. He said, writing of the disease as he had seen it in India, that despite the fact that unceasing searches have failed to identify an etiologic agent of infectious nature, sprue nevertheless behaves in many respects like an infection.

THERAPY

Liver Extract.—The use of liver in sprue goes back a good many years; Castellani says that it is an old native remedy in Ceylon. Manson and many of his distinguished successors had been employing liver soup for more than thirty years before recent reiteration of the many similarities of sprue and pernicious anemia freshly introduced liver therapy in its more effective forms. Under this treatment diarrhea ceases (Miller and Rhoads, in 1936, were the first to demonstrate roentgenologically the return of normal functional activity of the small intestine), all the other symptoms disappear and the patient rapidly takes on weight and returns to a completely normal status. It is nearly always necessary, however, to use larger amounts of liver extract than are required in pernicious anemia and the amount required to maintain the patient in good health must be individually determined in each case. The crude extracts are superior to the more concentrated preparations. In some fulminating cases it is necessary to give the extract by vein.

Rodriguez-Molina (1943), reviewing ten years' experience of the liver therapy of sprue in Puerto Rico, said that where the average life duration of the sprue patient was estimated at two years in former times it is now felt that the life expectancy of the patient who is receiving adequate treatment is that of the average person for the same age group, except that for individuals nearing fifty years of age the outlook is still not very favorable. Hanes (1942) emphasized the fact that now and then a patient is encountered who, though fulfilling the most stringent diagnostic requirements of the sprue syndrome, nevertheless responds poorly or not at all to therapy. He cited four such instances in sixty cases studied in the Duke Hospital Clinic; of the three patients who died, two were examined post mortem without finding an adequate explanation for the fatal outcome. Keele and Bound (1946), in their clinical survey of 600 cases of sprue seen in British troops in India during War II, felt obliged to conclude that our present methods of management and treatment are not curative and that even liver, nicotinic acid and riboflavin ameliorate only; they felt, however, that immediate prognosis for life under present-day therapy is good.

Folic Acid.—It having been found that the so-called vitamin M deficiency in monkeys that seems to be the approximate equivalent of the sprue syn-

ham, set about testing the new folic acid in sprue in man. The resu that the human disease was found to respond apparently as well to this therapy as to potent liver extract. It is said that three or four days after the use of folic acid is begun the patient usually volunteers the statement that he feels better and that by this time the reticulocytes begin to appear

in the peripheral blood, the tongue is less angry looking, a few new papillae are visible, gaseous distention is not so marked, and diarrhea is not so trouble-

in relatively good health for a number of months or years under adequate liver therapy, Suarez, Spies and Suarez (1947), in Puerto Rico, confirmed and extended the earlier observations of themselves and others on the efficacy of the agent. They found that the administration of small daily doses is more effective than many times as much given in a single dose, the daily oral administration of 10 mg. being adequate. They also found that a relatively small dose of folic acid accompanied by an adequate sprue diet produces better results than the administration of larger doses unaccompanied by an adequate diet. They gained the impression that 2.5 to 5 mg. daily would probably be found adequate as maintenance dosage for the majority of patients. Darby *et al.* (1947) found evidence of an improved ability to absorb vitamin A and carotene following therapy with folic acid, and Milanes *et al.* (1946) observed that patients with intestinal parasites responded to treat-

obtain satisfactory hematological responses in their cases, and that Comfort (1947) reported that at the Mayo Clinic their findings indicated that at least some patients do not respond in any particular as well to folic acid as to liver extract.

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(Lilly) one day and 4 cc. of parenteral vitamin B complex (Lederle) the next day, the injections being given intramuscularly into the buttocks and continued for three weeks or until clinical improvement was observed; thereafter vitamin B complex, at least one teaspoonful four times daily, was

beef) and liberalized this diet according to the improvement of the patient. Supplementary administration of vitamins A, B and C was made in about twice the amounts usually employed to meet the accepted daily requirements. Allibone (1946) concluded from a study of this employment of liver extract and B complex on alternate days in twenty-three cases that the strictness of the dietary treatment is ameliorated by this therapy in the milder cases but that in more severe cases it is not easy to demonstrate that it is of benefit. Brody and Gore (1946) reported the fine response to folic

TABLE 12.—SPRUE DIET

Breakfast

Toast, one thin slice
Fresh fruit, large serving
Eggs, 2 prepared in any manner desired
Skimmed milk, at least one large glass (this may be heated and used in place of cream for coffee or may be made into cocoa)

Lunch

Meat, large serving (½ pound at least)
[illegible]

Dinner

Fruit cocktail or tomato juice
Beef broth or any cream soup (make cream soups with skimmed milk instead of cream and omit butter)
Meat, large serving (½ pound at least)
Vegetables, 2 at least
Desserts, as for lunch
Skimmed milk, one glass

Eggnogs, skimmed milk or fresh fruit may be eaten between meals

The diet should consist largely of protein:
Meat Meat should always be lean and rare
Beef, lean, either roast or steak
Lamb, lean, either roast or chops
Ham, lean
Liver, tongue, heart, kidney or sweetbreads
Fish, any fresh fish
Chicken
Lobster, crab or oysters
Milk and milk products skimmed milk, buttermilk and American and cottage cheese
Eggs prepared in any manner desired

All fatty foods should be avoided butter, cream, lard, olive oil and all oil salad dressing, avocado pears, pie, pastry and all foods fried in fat
All starchy foods should be avoided potatoes, beans, corn, bread, cereals, cake and candy
(Barker, 1943)

acid of a child of seventeen months, dosage beginning with 25 mg. by mouth per day and being later reduced to 10 mg. per day; the patient had failed to respond to intensive therapy of the type just described. Dalton *et al.* (1946) reported excellent results in two cases of celiac disease using only 5 mg. of folic acid daily, but Davidson *et al.* (1947) failed to obtain good results in their three cases even with as much as 20 mg. daily.

Vitamin K.—Very interestingly, there have been reported several cases in which there has been developed a bleeding tendency correctable by ad-

ministration of vitamin K (see Vitamin K Deficiency). Kark *et al.* (1940)

Iron.—Observers have pointed out the necessity of adding iron to the regimen when the anemia is microcytic throughout or is converted from macrocytic to microcytic by liver therapy.

Calcium, Vitamin D, Parathyroid Extract.—Whatever may be the cause of the calcium deficiency of the blood in specific instances—whether there is actual faulty absorption or only excessive loss through the utilization of much calcium to form soaps with the fatty acids in the intestine—the necessity to attempt to supplement the supply is oftentimes quite apparent; indeed, in the series of patients studied by Bassett *et al.* (1939) prolonged liver therapy failed to cause improvement in the absorption of calcium, phosphorus, nitrogen, or fatty acids; moderately high levels of calcium intake did not consistently produce a positive balance in the blood, but when vitamin D was used in addition calcium absorption was obtained. The methods of administering calcium are given under Tetany, vitamin D under Rickets—of the latter preparations viosterol or drisdol are to be preferred since the fish oils will be poorly absorbed. Intensive ultraviolet light therapy is valuable also Parathyroid extract should be used very warily since it increases blood calcium only by depleting the bones It is of interest to note that Batavia powder, the ancient "Peter Sys's Cure" extensively used in Singapore in the old days and still somewhat employed in the East generally, is a proprietary preparation of lime, principally ground cuttlefish bone, I believe.

PERNICIOUS ANEMIA

(See the Section on Anemias)

TETANY

The syndrome to which this name is given is characterized principally by carpopedal spasm, *i.e.*, a tonic spasm in which the hands assume the so-called accoucheur position with the fingers and thumb approximated and with contracture at the wrist, the arms are often held against the chest and if the lower extremities are involved there is flexion at the knee joint with the feet in the position of equinovarus. There are also generalized convulsions which start in the eye and face muscles and involve the whole body, with consciousness returning as soon as relaxation takes place. Laryngospasm,

galvanic current elicits signs of hyperexcitability of the peripheral nerves (Erb).

By far the most frequently seen of the tetanies is that so often associated

with rickets in young children, a type most likely due to decreased absorption of calcium in the absence of sufficient vitamin D. The tetany of sprue is probably also a result of failure in calcium absorption. Frank tetany during pregnancy and lactation occurs but is rare, though tetanoid manifestations such as irritability, painful cramps in the legs, insomnia, transient paresthesias and edemas are of common occurrence. This type is of course easily assumed to be due to loss of calcium, first to the fetus and then in the milk, but it is possible at least that pregnancy and lactation are merely the factors that uncover a latent tendency to parathyroid deficiency. True postoperative tetany is not often seen nowadays but its occurrence is not reckoned a mark of poor surgery since the parathyroid glands are often eccentrically located and also apparently succumb easily at times though not considerably disturbed. In conditions of persistent vomiting and where too much alkali has either been ingested or injected, there occurs a tetany associated with the state of alkalosis. Another sort of alkalotic tetany is that resulting from great loss of carbon dioxide through abnormally rapid breathing, as occasionally seen in hysterical or otherwise psychically ill persons; Ellsworth and Sherman (1936) recorded the occurrence of hyperventilation tetany during an asthmatic attack and Musselman (1945) said it occurred frequently in the Cabanatuan prison camp during War II in men who reacted hysterically with hyperpnea as a result of misinterpretation of symptoms through the experience of disease and death all about them. A type of "idiopathic" tetany in adults is recognized—a group of cases in which none of the above etiologic associations seems to apply; however, this group is probably even much smaller than is commonly believed, most of the cases probably being classifiable under the infantile type due to vitamin D deficiency. It is further worthy of note, perhaps, that among the small number having no discernible cause other than a spontaneous parathyroid deficiency (comparable to the thyroid deficiency in true myxedema), diarrhea is often present though without the other symptoms of a fully developed case of sprue. Unquestionably tetany appears transiently at times at the height of serious toxic attacks, such as acute poisoning or a febrile state.

The statement, formerly frequently made, that tetany does not occur in the newborn (i.e., under two months of age) has had to be revised, for such cases have been increasingly reported, some authors seeing several cases in a year's practice. Kendig (1942) referred to twenty-seven cases in the literature and included four of his own. It seems likely that tetany in the newborn is due in most instances t[illegible] glands, but Zahorsky (1937) [illegible] prelacteal feeding of alkaline mixtures [illegible] [illegible]ition had undoubtedly developed in utero for the baby was born with every one of the symptoms of tetany and responded dramatically to the therapeutic test; he felt that many cases of so-called "birth trauma" might well have been diagnosed tetany and treated as such. McCarrison has described a form of tetany in adult natives of the Himalayas, in association with goiter; it is probably the dietetic, infantile type, for upon removing to a different locality spontaneous recovery occurs.

In all of the above types of tetany there is a disturbance in calcium metabolism, with decrease in blood calcium during the period of active symptoms and rise in the same as improvement takes place, in all, that is, except the gastric, bicarbonate and hyperpneic forms, in which there is a state of alka-

losis but normal blood calcium. To explain this discrepancy, we assume that the important matter in tetany is not how much calcium there is in the blood stream but how much of it is ionized; a shift to the alkaline side is thought to decrease ionization This may be a correct explanation, as it is certainly a serviceable one, but the fact is that there has not yet been devised a method for determining the amount of calcium ion in the blood, and the assumption that it is equivalent to the amount of diffusible calcium can be justified only upon the score of convenience Since calcium deficiency and the full symptomatology of tetany are not necessarily parallel phenomena, and because chronic

only be properly interpreted in conjunction not only with the inorganic phosphorus but with the serum protein also Tetany does not occur characteris-

Miller (1944) reported a case of tetany he felt to be caused by a low plasma magnesium content occurring in a child of six years who also had osteochondrosis of the capital epiphysis of the femur (Legg-Perthes disease)

The first empiric use of calcium in tetany was probably that of Walter Harris, of London, who in 1689 "accomplished cure with no other medicines than a few ounces of crabs' eyes mixed with crystals of tartar." Shelling (1932) stated that among Negroes of the eastern shore of Maryland the use of shells in the treatment of this disease has been handed down in some instances as a family secret through several generations The first rational employment of calcium as an anticonvulsant was that of the Italian, Sabbatini, in 1901.

THERAPY

Calcium Salts by Mouth.—There has been an unfortunate lack of under-

i e, taken in tablet form or stirred up in milk. Therefore calcium chloride has been used because its acidity promotes its absorption But this salt may induce acidosis and is capable of causing serious damage to the gastro-intestinal tract.

work of Roe and Kahn, in 1927, in which they showed that a 91 per cent rise in blood calcium could be obtained in the human by the administration of 75 grains (5 gm) of calcium lactate dissolved in water as against only a 28 per cent rise when the same dose was given hourly for eleven hours (a total of 55 gm) dissolved in milk It would seem that we have been giving calcium salts

improperly by mouth and that for best effects they should be given dissolved in considerable water; and furthermore, that when so used calcium lactate is likely to give as good account of itself as calcium chloride or calcium gluconate.

Adult dosage of calcium salts is usually 90 grains (6 gm.) or more distributed throughout the day Sometimes ammonium chloride is also given to increase the ionization of calcium, 75 grains (5 gm) or more daily in divided doses. Dilute U S P. hydrochloric acid may be used in the same way, a teaspoonful (5 cc.), well diluted in water or milk, four to six times daily. It has been stated that the use of half as much lactose as calcium lactate per dose promotes the absorption of the latter, but there is not apparently much confirmation of this in clinical experience.

McGavran (1932) handled his patient, born with tetany, as follows: "Calcium chloride, 7 grains (0 45 gm.) every hour, viosterol, 3 drops every two hours, phenobarbital, 1/12 grain (0.005 gm) every four hours. Forced feedings, 1 ounce of breast milk, every hour, were administered with a medicine dropper It took forty-five minutes out of every hour to get the ounce down. In twenty-four hours the calcium chloride was stopped as it produced vomiting The phenobarbital was stopped in forty-eight hours In ten days the baby became a simple feeding problem and has developed so far into a perfectly normal healthy twelve months old baby."

Calcium Salts by Injection.—Under urgent circumstances such as severe convulsions and glottic spasm, *5 to 20 cc* of a *5* per cent solution of calcium [illegible]

injection of calcium gluconate in the treatment of tetany of the newborn has been reported several times Shannon (1938) reported two cases in which calcium salts were not only precipitated at the sites of injection but also at remote points in the body; reabsorption eventually occurred in both instances without known permanent damage, but in Lamm's (1945) three cases abscesses occurred at the site of injection and one of the infants developed sepsis and died.

Viosterol and Fish Oils.—These vitamin D preparations are used routinely in all infantile cases, there are reports of their satisfactory employment for the promotion of calcium absorption in various other forms of tetany also. (See Rickets for methods of using these agents.) Very interestingly, Sevringhaus and St John (1943) successfully replaced dihydrotachysterol (*see below*) with high vitamin D therapy in six women with permanent and severe hypoparathyroid tetany, the duration of the treatment being two years or longer in four of the cases The doses varied from 150,000 to 400,000 U S P. units daily; calcium salts were also given by mouth. Dietary restrictions previously considered necessary were withdrawn and the patients were allowed to take as much meat, eggs and milk as desired in spite of the higher phosphorus intake involved

Dihydrotachysterol (A.T. 10).—This agent is a chemical substance derived [illegible]

calcium absorption from the gut and phosphorus [illegible]

The drug has been used successfully in *postoperative* parathyroid tetany,

in chronic idiopathic tetany and in tetany of the newborn. Dihydrotachysterol is available commercially in the form of a solution known as hytakerol, each cc. of which contains the equivalent of 1.25 mg of crystalline dihydrotachysterol; capsules of hytakerol are also available containing the equivalent of about 0 625 mg. of the crystalline substance in oil. In severe cases of postoperative tetany some men have used as much as 10 to 20 cc. daily for a few days and then sharply reduced the dosage, but Ryan (1940) probably expressed what by now is the consensus in saying that in most instances even of severe tetany the dose should not exceed 2 cc daily; subsequently the maintenance dosage must be worked out in each case, some individuals require from 0 5 cc. upwards daily, others do well on very small dosage only once or twice weekly. In his case of tetany of the newborn, Bloxsom (1940) was obliged to use 15 drops three times daily in order to initiate improvement. If calcium is given by mouth in addition, dihydrotachysterol dosage can be much reduced

This is a dangerous drug because it can easily cause hypercalcemia (see symptoms under Parathyroid Extract, below) and it should not be used in the present state of our knowledge unless frequent observations can be made of the blood calcium and phosphorus levels

Parathyroid Extract.—Though probably soon to be more or less completely replaced by dihydrotachysterol (see above), this drug has until recently been the one of choice in resistant cases of postoperative tetany. It is always supplemented by large doses of calcium by mouth In severe cases with serum calcium values as low as 5 mg per 100 cc. (the normal is 10 to 11 mg), from 40 to 60 units may be given intravenously and half the dose subcutaneously or intramuscularly four to six hours later. Probably in most cases, 30 to 40 units daily will maintain the serum calcium at normal after this level has been reached, but the action varies markedly in different individuals, and in many cases an immunity develops after a few weeks so that even much increased doses are ineffective in influencing the blood calcium or phosphorus Shelling and Goodman (1934) believed that in such instances we are not dealing with resistance to parathyroid but rather with factors conducive to increase in the intake of phosphorus, upon the basis of very satisfactory experience in two cases, they recommended the trial of low phosphorus diets in parathyroid tetany. Boothby and Davis (1936) also favored the use of such a diet, plus calcium salts in large doses with adequate amounts of vitamin D, and only

indicated, the fault here is not in parathyroid insufficiency and therefore if the extract is to be used it must be fortified with full doses of calcium

the blood calcium should be made Later there is increasing listlessness, perhaps high fever, and finally coma. Other than immediate cessation of the injections, the treatment rests upon a very insecure foundation Lowenburg and Ginsburg (1932) employed venoclysis to aid excretion of calcium and possibly also of parathyroid extract and to dilute the blood, which, at least in animals,

becomes very viscid and markedly decreased in volume. The administration of calcium at the same time in order to prevent decalcification seems rational

The Treatment of Alkalotic Cases.—In these cases of course the principal indication is to overcome alkalosis, which is usually easily accomplished if overdosage of alkalis has been at fault. Where loss of chlorides through vomiting obtains, physiologic solution of sodium chloride must be given in large quantities by all the usual channels. Ammonium chloride may be given by mouth, or intravenously in amounts of 300 to 500 cc. of 0.82 per cent solution, first testing the solution, as recommended by Cantarow, to see whether it causes hemolysis. In the hyperpneic cases there is often difficulty in controlling the causative factor, namely, the hysterical attacks of rapid breathing in psychically disturbed individuals. In one such patient, when an attack had been precipitated by excitement, Meakins (1930) proved that alkalosis was the causative factor by producing instantaneous remission when the patient was caused to inhale a mixture of 5 per cent carbon dioxide and 95 per cent oxygen. The paper-bag method (see Hiccup) might be expected to appeal to such patients.

Treatment of Tetany from Magnesium Deficiency.—In Miller's case, previously referred to, the patient, who was six years of age, was given 5 grains (0 3 gm.) of magnesium sulfate by mouth three times daily; striking symptomatic results were said to have been obtained.

XEROPHTHALMIA

(*Vitamin A Deficiency*)

This entity is characterized principally by night-blindness (hemeralopia), changes in the skin, and certain corneal symptoms, to which last is applied ... mic the victims ... ssive difficulty ... the disease; in rats deprived of vitamin A in the diet, the disturbance has been shown to be due to failure of regeneration of visual purple in the retina. The later gross signs and symptoms are redness of the eyes, lacrimation, photophobia, pain in the eyes, wrinkling of the conjunctiva, and failure of vision associated with yellowish-white areas on the cornea, which spread until the entire cornea becomes uniformly hazy and insensitive and finally necrotic and ulcerated. A rather large variety of skin abnormalities has been found associated ... hyperk ... and als ...

... gyp- ... lacia ... 1827. ...

and the British Solomon Islands, ... During War I it became a serious problem Africa, Yucatan and British Guinea. During War I it became a serious problem in Germany and Austria and was also widespread in Denmark, the incidence in

are also excellent, but viosterol, drisdol and ultraviolet irradiation are *worthless, since it is not vitamin D that the patient is lacking.* Vitamin A is not yet clinically obtainable in pure form, but carotene has been made available. The Council-accepted products for clinical use are carotene in cotton seed oil, carotene with vitamin D concentrate in oil and capsules containing vitamin A obtained from fish liver oil. The capsules contain 25,000 U.S.P. units of vitamin A or about five times the daily requirement as laid down by the National Research Council; the carotene in oil contains 7,500 units of vitamin A per gm. and is dispensed with a dropper designed to deliver 25 drops to the cc. Youmans (1939) has seen a few cases in which there was a brief exacerbation of the symptoms when use of these highly fortified oils was begun. Kirwan *et al.* (1943), in Calcutta, have introduced vitamin A parenterally, but Cienfuegos' (1946) results indicated that the vitamin is not utilized at all when given in this manner.

Josephs (1944) reported a case of severe hypervitaminosis A occurring in a boy of three years who had received about 240,000 U.S.P. units of vitamin A daily since he was about three months of age. The condition was characterized by hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development, ... hair; it was accompanied with an ... Most of the ... d from the ... pt that in addition there occurred pain and localized periosteal swellings; this case was apparently due to the ingestion of one to two teaspoonfuls daily of percomorph liver oil with viosterol. Gerstle (1945) reported a case in which "pin-point" miosis apparently resulted from the taking during a two-week period of 250,000 units of vitamin A daily, this severe miosis being unassociated with any diminution of night vision and the pupils returning to normal size five days after discontinuance of the excessive taking of vitamin A

VITAMIN K DEFICIENCY

(Hypoprothrombinemia)

... principally in Denmark and the United ... umstances under which ... unt necessary to insure ... the vascular system. It has furthermore been determined that these instances of hypoprothrombinemia are principally the result of deficiency in vitamin K, a factor essential ... of the liver of the substance, prothrombin, without which ... Mammals including man obtain this vita- ... it is a dietary constituent, being present ... as alfalfa and spinach, and in ... wer, kale, ... wer bowel ... herapeutic ... ciencies of use in the form of pure synthetic compounds ... clinical significance are seen under the following circumstances

Liver Disturbances.—The liver is of great importance in the maintenance of a normal prothrombin level for two reasons: first, it is the site of the formation of prothrombin, a synthesis in which vitamin K, absorbed from the gastro-intestinal tract, plays a vital part; and second, vitamin K is a fat-soluble substance that is poorly absorbed if the liver does not pour sufficient bile into the intestine The bleeding tendency both in obstructive jaundice and in cases of biliary fistula is now recognized to be due to hypoprothrombinemia, the absorption of vitamin K being reduced in the first instance by the reduction in the amount of bile reaching the gut, and in the second instance by the diversion of bile from the gut. Further than this, it now seems that hypoprothrombinemia can result from liver disease *per se*, that is, without a sufficient depression or diversion of bile to prevent adequate vitamin K absorption—for example, in some instances of infarction, liver abscess, or cirrhosis. It is assumed that the bleeding tendency in these instances is due to the inability of the liver to form prothrombin even though ample vitamin K is being absorbed from the gut.

Gastro-intestinal Disturbances.—At the Mayo Clinic there has been studied a series of patients with intestinal lesions of a diverse nature: intestinal obstruction, postoperative gastric retention, sprue, chronic ulcerative colitis, internal and external fistulae. In some of these cases hypoprothrombinemia and its consequent bleeding tendency were found, the fault lying apparently in an insufficient amount of normal intestinal mucosa for adequate absorption of vitamin K, insufficient absorption as a result of fat-poor dieting in the sprue cases, prolonged diarrhea, or long-continued aspiration of duodenal contents. Others have reported similar findings.

Nutritional Deficiencies Other Than Sprue.—Kark and Lozner (1939) reported four patients each having a dietary deficiency disease apparently unassociated with any liver disturbance; in each there was hypoprothrombinemia. Scurvy was diagnosed in three of these cases and pellagra with subclinical scurvy in the other. It is difficult to understand how the mere taking of a diet deficient in vitamin K could reduce the plasma prothrombin since the bacteria in the lower bowel are able to form the vitamin from food residues entirely devoid of it. However, Warner and Owen (1942) found that patients in pernicious anemia relapse frequently manifest hypoprothrombinemia that does not respond to vitamin K administration but disappears when liver therapy is instituted, and the interesting idea of Benesch (1945) regarding bacterial equilibrium in the intestine has already been discussed in the article on Pellagra.

Hemorrhagic Disease of the Newborn.—It is now established that the prothrombin level of the blood of newborn infants often drops rather precipitously during the first days of life and is then restored spontaneously. The hemorrhagic episodes occasionally seen during the first few days are generally looked upon as due to this hypoprothrombinemia, which Waddell and Guerry (1939) were the first, I believe, to show could be effectively both treated and prevented by the administration of vitamin K. Quick and Grossman (1939) offered as explanation of this type of hypoprothrombinemia the hypothesis that very little storage of prothrombin or of vitamin K takes place in the fetus, that exhaustion of this small amount quickly occurs after birth, and that the build-up toward the normal and safe quantity only begins with the establishment in the intestine of bacteria that synthesize the vitamin, which, in the presence of bile, is then absorbed. Salomonsen and Nygaard

(1940) showed that if small feedings of breast or cow's milk are begun two hours after delivery in order to form a nourishing substrate for the organisms rapidly entering through the mouth and the anus, hypoprothrombinemia of the newborn can be almost completely prevented. In Sweden, Lehmann (1944) has made a large scale application of vitamin K prophylaxis covering 13,250 newborn infants who were given the vitamin and 17,740 untreated controls. He found that about 1.6 full term infants per 1000 treated were saved by the treatment, concluding that if in Sweden, with 100,000 full term infants born annually, there were a general employment of prophylactic vitamin K, 160 infants might be saved yearly. In the United States, Waddell and Whitehead (1945) reported that over 4000 infants born at the University of Virginia Hospital had received vitamin K prophylaxis and that hemorrhagic disease had disappeared from their nurseries in contrast to the incidence of hemorrhagic disease in the newborn of 0.3 per cent prior to the routine use of vitamin K; this figure of 0.3 per cent is about that generally stated as the usual incidence of this syndrome. But there is apparently a reverse to this coin, for Potter (1945) reported the results of a four-year study during which 6560 infants were born to mothers receiving vitamin K and 6630 to mothers who did not receive vitamin K; the mortality rates for live-born infants were identical in the two series as was also the number of infants who showed evidence of hemorrhage on postmortem examination. Potter concluded that one is justified in expecting no decrease in infant or fetal mortality to result from the routine administration of vitamin K to all women during labor. Parks and Sweet (1942), and Sanford et al. (1942), in earlier studies, had also been unable to show that hemorrhagic manifestations in the newborn were associated with a prothrombin deficiency or that they were de- [illegible] tamin K; these observers maintained that [illegible] ficiency were responsible for the majority [illegible] he newborn. However, Quick (1947) has expressed the opinion to me that despite the fact that these infants do not bleed as long as their vascular system suffers no injury, the prothrombin may be startlingly low and he feels that they are therefore in constant danger since any injury that is too severe to be handled by the vascular response will lead to uncontrolled bleeding, he therefore looks upon the administration of vitamin K to the mother as a prophylactic measure which should be obligatory. Quick has also made the point that if the newly-born infant requires a surgical operation it is imperative that vitamin K be given preoperatively and continued daily until the baby again feeds regularly. Nevertheless, it begins to appear that in some instances of hemorrhagic disease of the newborn, hypoprothrombinemia is not responsible for the bleeding. Scobbie (1942) reported five cases in which she said the prothrombin levels were relatively high. Allibone and Baar (1943) accounted for one case on the basis of congenital fibrinopenia and another on the basis of transient afibrinogemia, while Baar (1941) wrote of a qualitative platelet defect.

Idiopathic Hypoprothrombinemia.—It is difficult to know just where to place such cases as the following. Rhoads and Fitz-Hugh (1941) described an eighteen-year old patient with a hemorrhagic diathesis extending throughout most of his life, the defect appearing to be due to an "idiopathic" hypoprothrombinemia coupled with an abnormality of the fibrinogen. Plum (1943) also reported cases of two young otherwise perfectly healthy and normal individuals who had prothrombin levels of 34 and 50 per cent of

disease in an adult that they were unable to identify with any recognized pathologic entity; the prothrombin values in this case showed phasic fluctuations that were not correlated with therapeutic efforts and the amount of liver damage found at autopsy was felt to have been too small to cause the hypoprothrombinemia.

THERAPY

The oldest of the Council-accepted synthetic vitamin K preparations is menadione (thyloquinone), which is available in 1 and 2 mg. capsules and tablets for oral administration and in ampules in solution in oil for intramuscular administration. Menadione is rapidly absorbed from the gut in the presence of bile and therefore to assure that there be plenty of bile present in all instances it is the usual practice to give one or two 4 grain (0.25 gm.) tablets of dehydrocholic acid (decholin) together with the menadione in order to insure its quick absorption, though this is not absolutely necessary. When giving the agent intramuscularly of course the bile salts are not used. The newer Council-accepted preparation is menadione bisulfite, a water soluble salt, available in the form of tablets with a content equivalent to 2 mg. of menadione and also in ampules in aqueous solution for intravenous administration, each cubic centimeter of the latter is equivalent to 2 mg. of menadione. Three other vitamin K preparations that are not yet Council-accepted but that seem to be valuable additions to the armamentarium are hykinone, synkayvite and synkamine. Shapiro (1947) has well made the point that the various vitamin K preparations on the market do not exhibit the same vitamin K activity and suggests that for uniformity and simplicity

synkayvite 490 units. Therefore if one takes 2 mg of menadione as the average dosage level, one should apparently give 3.2 mg of hykinone or 4 08 mg. of synkayvite. Quick (1947) says that generally 2 to 5 mg. of menadione or its equivalent daily is sufficient for prophylactic purposes, but that in cases of severe postoperative bleeding due to hypoprothrombinemia the water-soluble preparation in a dosage of 10 mg. should be promptly given either intramuscularly or intravenously.

studies for ten or more days postoperatively because of the likelihood of a postoperative fall in prothrombin and the beginning of severe bleeding Unfortunately, patients are not infrequently seen who respond very sluggishly or practically not at all to vitamin K therapy, and a severely damaged liver does explain all these cases because patients have been seen who by every known clinical and laboratory test were convicted of hepatic insufficiency and who were nevertheless able to utilize vitamin K and maintain a normal plasma prothrombin level.

There are no peculiarities of hypoprothrombinemia due to gastro-intestinal disturbances requiring special mention from the standpoint of therapy except

that of course in some of the cases absorption of the vitamin may not follow its administration by mouth.

In employing vitamin K to prevent the "physiologic" hypoprothrombinemia of newborn infants it is the practice either to give 2 mg. of menadione, or

mother and child and that this decrease can be prevented by the administration of menadione during labor; Hardwicke (1944), however, was unable to confirm the depressant effect of the barbiturates.

The studies of Lawson (1941), and Willumsen *et al.* (1941), indicated that intramuscular injections of whole maternal or paternal blood in the usually employed quantities of 10 or more cc. at four- to eight-hour intervals have very little effect in combating the hypoprothrombinemia of the new born; even intravenous transfusion is much less effective than vitamin K administration.

ENDOCRINE DISTURBANCES

ENTITIES WHICH SHOULD BE LEFT TO THE SPECIALIST

There is a great stir in the field of endocrine investigation nowadays, with the result that much hullabaloo has been raised to favor the extensive employment of commercially available "hormone preparations" in treatment of the endocrinopathies. The result is that those of us who are brash and immodest enough to write books are being constantly appealed to with the plea to "straighten out" these matters—which usually means these commercial products—for the general practitioner. Sitting in the meetings of the endocrinologists, listening to the conversations of some of my friends who are of that persuasion, studying the literature, rolling things around in my mind, I come to the conclusion that most of the endocrinopathies are still susceptible of satisfactory handling only in consultation with, or entirely by, specialists in that clinical field. These gentlemen do sometimes accomplish quite satisfactory results, but no one is better aware than are they themselves what a prodigious expenditure of time, what an exhibition of diagnostic acumen derived from their special training, and what an amount of frank but cautious and above all expertly calculated therapeutic tinkering is required for them to arrive at such goals as they achieve. The following, in addition to an increasingly large group of entities whose very names ring queerly in the ears of an ordinary medico, are best left alone by the general man, in my opinion: acromegaly, Simmonds' disease (pituitary cachexia), pituitary dwarfism and infantilism, Fröhlich's syndrome (adiposo-genital dystrophy), Cushing's syndrome (pituitary basophilism), pituitary habitual abortion, pituitary bilobar disorders, pituitary

syndrome

ENDOCRINE THERAPY IN MENSTRUAL DISTURBANCES

(See *Menstrual Disturbances*)

CRETINISM

[illegible]

most prevalent in goitrous regions, though curiously enough it is relatively rare in North America; however, with regard to this last point, Stoddard's (1933) study indicated that in Wisconsin, and by inference in other Great Lakes regions and in the Pacific Northwest, the state of endemicity of cret-

inism is probably quite imminent. Among preserved records the first reference to cretinism is that of Paracelsus, in the sixteenth century, though of course the entity must have been prevalent long before that period.

Most patients do not come under observation until they are six to eight months old because failure to develop normally is not often noticed before that age. In typical cases the general appearance is characteristic ...
the
witl
tanels remain open, the forehead is low, the abdomen is large, and there is often an umbilical hernia; bony growth is delayed, but the hands and feet are large and the toes and fingers short and thick; dentition is delayed, temperature is subnormal, the skin is dry and the tissues have a doughy feel but do not pit upon pressure. Constipation is the rule. Cretinous individuals are undersized physically and very much stunted mentally. Their characteristic response to questioning is a wrinkling grin, and their ultimate mental development is usually into a clownish sort of childishness in which they seem very happy; any type of idiocy, however, may be seen The state of untreated cretinism is not incompatible with attainment of full years, but most victims of the affection succumb fairly early to one of the infectious diseases.

THERAPY

The response of cretins to the administration of desiccated thyroid substance (*nota bene:* this substance is not an extract, therefore the term "thyroid extract" is not permissible; see also the note regarding differences in brands in Myxedema) is well known to everyone. One needs but to start with a small

... twice daily and increases as necessary to get
... weight and
... and hard to

fever; when such symptoms occur, the drug should be omitted for a few days to a week and then resumed with a dose ½ grain (30 mg.) lower than that previously given. Wilkins did not consider the apparent disappearance of all clinical symptoms as an adequate criterion of the adequacy of thyroid therapy, being guided rather by the degree to which the "bone age" and "height age" of the patient keep pace with the normal. Unless there is continuous rapid development of the osseous system it is felt desirable to increase thyroid ... if the bone age exceeds the normal or

and growth ceases. It seems rarely to be necessary to exceed a dose of 3 gr. (0.2 gm.). ... individuals ranging in age from sixteen to

nosis for normal mental attainment is not as good as for physical development.

As a result of their study of twenty-nine cretins, Brown *et al.* (1939) said "a small proportion" of them may attain normal mental development. Bruch and McCune (1944), basing their opinion on a statistical examination of the data from the study of twenty-three patients, said they were persuaded that one must be cautious in predicting the intellectual future of congenitally hypothyroid children, irrespective of both the time at which treatment is first *instituted and adequacy of the treatment as judged by physical criteria.* In 1936, Kerley last reviewed a case on which he had several times previously reported: a woman of thirty-five who was competently treated from the age of two months but in whose mental development there were such gaps as inability to compose a letter or to attain any appreciation of mathematics, she was able to read and write but when engaged at the latter inserted words having no meaning in the context, she had worked for many years in the same low-grade employment because unable to take promotion

Bruch and McCune (1944) warned that whereas intensive treatment is warranted during a trial period, the fact must be kept in mind that overdosage can cause serious disorders of behavior, and that unless such dosage is clearly productive of proportionately improved mental development, the social and emotional problems it may engender must not be ignored

MYXEDEMA AND HYPOTHYROIDISM

Spontaneous myxedema is a chronic affection associated with gradual fibrosis and atrophy of the acini of the thyroid gland and characterized by impaired mentality, over-growth of fat and connective tissue, and pronounced change in appearance. The disease occurs all over the world, but is most prevalent in goitrous regions. It is usually seen in women at about the time of the menopause but approximately one-eighth of the cases occur in men and a very small number in children Of the cause of the thyroid shrinkage practically nothing is known, it is said that the disease has a familial tendency

In the usual case of myxedema the first symptom is a gradually increasing mental sluggishness combined with a feeling of physical weariness not appeased by any amount of resting. The face assumes a coarsened, masklike expression with often a transverse furrow across the forehead and an area of brownish pigmentation over the cheeks The skin is dry and scaly and the hair falls out. The false edematous deposits, which do not pit upon pressure, occur in all the subcutaneous tissues, making it appear as though the patient has stored up much fat, the extremities are chiefly affected, however Lange (1944) ascribed this edema to a marked increase in capillary permeability and it seems that his findings have been confirmed The temperature is below normal, there is a secondary anemia and a reduction in pulse and basal metabolic rates, and the

age coincided with the appearance and the control of the myxedema, the

opportunity having existed in this case to compare pertinent cardiovascular observations before the appearance of myxedema with findings at the time myxedema was discovered and also after more than two years of control. Latterly, evidence has been accumulating to show that myxedematous individuals are unusually prone to develop arteriosclerosis, chronic nephritis, arthritis, fibrous myocarditis and coronary sclerosis, but since the age of onset of many of these conditions coincides closely with that of myxedema, it is going to require very careful work to establish the inter-relationship

In recent years a number of observers have been calling attention to the

stance they may be underweight and not sensitive to cold or suffering from a marked dryness of skin; indeed they may not even feel mentally sluggish, though they nearly always grow inordinately tired by the end of the day. Menstrual or abdominal disturbances of many types, habitual abortion or sterility, or rheum[illegible]
is more often mad[illegible]
that this may be [illegible]
objective signs that ultimately cause women to seek medical help Thurmon and Thompson concluded a number of years ago that if in suspected cases of hypothyroidism without frank myxedema the depression in basal metabolic rate is less than 21 per cent below the average normal, underfunction of the thyroid is usually not present. But that has not been the subsequent experience, at least here in t[illegible]
his experience in [illegible]
dramatic when th[illegible]
indeed this accords with the experience of Davis (1943), in Delaware, where he found much more hypothyroidism than had been suspected to be present.

THERAPY

In the summer of 1891, Murray described before the British Medical Association the first case of myxedema ever treated by the administration of the thyroid gland of the sheep. Since the reporting of this classic case, many thousands of patients have been thus treated and cured (Burgess', 1946, [illegible] thyroid therapy in 1892 at the age of thirty-nine when she [illegible] d to be satisfactorily [illegible] it has now become apparent that such failures to restore the patient to complete health as do occur are due to one or more of the following factors.

(a) *The use of a nonpotent specimen of the drug.* Hunt, corroborated by Means (1933), and Lerman and Salter (1934), showed that there may be a great variation in the strength of the drug as prepared by different manufacturers, a fact that certainly places the practitioner with his occasional case of this disease in a quandary. The only practicable solution of this difficulty is to determine the dosage with a particular preparation solely upon the basis of therapeutic results. Thyroxin is more expensive than the desiccated gland substance and not as reliably effective; it may be given by mouth or parenterally.

(b) *The beginning of treatment too late in the disease.* It is the exceptional individual with far advanced myxedema who completely recovers under even the most careful treatment.

(c) *Lack of cooperation upon the part of the patient.* After a considerable degree of recovery has taken place very many individuals refuse to continue with the proper thyroid dosage required to complete and maintain th [illegible]

(d) [illegible]

the res[illegible]

palpitation, sleeplessness, dyspnea, excessive warmth, dizziness, nausea), are evermore reluctant to take sufficient doses to maintain them in a normal condition.

Thyroid Dosage in Myxedema.—It is usual practice to begin with a dose of 1 grain (60 mg), or only 1/2 grain if the patient is arteriosclerotic or has coronary disease, McGavack *et al.* (1945) said that thyroid therapy must be very cautious in cases complicated with cardiac failure, the dose being sufficiently small to avoid an aggravation of the cardiac phenomena. In all cases, whether complicated or not, increases in dosage are made very gradually in order to add slowly to the amount of work required of the heart and the load upon the vessels; in average cases in Thompson's (1939) considerable experience 1½ to 2 grains (0.1 to 0.13 gm.) have sufficed for maintenance; Shorr (1944) said that in no case of complete myxedema at the New York Hospital has more than 3 grains (0.2 gm) been required. Since in hypothyroidism serum iodine is characteristically subnormal, Winkler *et al.* (1945) felt that serum iodine is not only a valuable aid in diagnosis but also a useful criterion of the adequacy of treatment with thyroid substance, for the basal metabolic rate in their experience responded much more slowly to alterations in thyroid status than did the serum iodine, certain it is that factors other than thyroid medication obviously affect the basal metabolic rate since it varies from time to time without change in the dose of thyroid. McGavack *et al.* (1945) felt that a decrease from the initially high capillary permeability is one of the earliest and most constant signs of improvement and is therefore a useful guide to therapy.

Since thyroid substance acts very slowly there seems no point in giving divided dosage throughout the day, though some patients feel they experience palpitation and difficulty in getting to sleep if they take their daily dose later than mid-afternoon. Tolerance to thyroid substance apparently never develops even after years of medication, but Hamblen (1946) has described as thyroid "addiction" a state of affairs in which a normal patient has been given large doses of thyroid empirically and experiences a characteristic train of symptoms upon withdrawal of the thyroid medication; a basal metabolic test done four to six weeks after withdrawal in such cases may be quite low and the inference commonly drawn is that the original presumptive diagnosis of hypothyroidism must have been correct, and accordingly the patient is started again on thyroid medication—but Hamblen says that what actually has happened is that the empiric thyroid therapy has depressed the intrinsic function of the thyroid gland and produced a pharmacologic hyperthyroidism.

Thyroid Dosage in Hypothyroidism without Myxedema.—The dosage here is about the same as in true myxedema.

Auxiliary Therapy.—The eruptions or other reactions that sometimes accompany thyroid therapy in the beginning can at times be avoided by the

that the American Medical Association, the American Public Health Association, and the Federal Food and Drug Administration cooperate to give the entire country a natural salt containing 0.01 per cent potassium iodide or its equivalent. He feels that the term "iodized" should be eliminated at once and that emphasis should be placed on the use of a whole salt or natural salt to prevent food deficiencies. It does certainly seem disgraceful that any goiters at all are still seen, for it is the belief of those most qualified to have an opinion on this subject that the universal ingestion of the requisite small amount of iodine would practically completely eliminate the development of goiter in pregnancy, *in utero*, and in childhood. The danger of inducing thyrotoxicosis through the prophylactic ingestion of iodine is so small that it cannot be taken into practical account.

THERAPY

The treatment of simple goiter by the same method as employed in prophylaxis sometimes accomplishes an astonishing diminution or even total disappearance of the enlargement. However, the cases of long-standing goiter that are favorably affected are very few. Up to sixteen or seventeen years of age the response is better; in Marine and Kimball's studies in Akron, Ohio, of 1182 children with goiter at the first examination who took iodine, 773 thyroids decreased in size, while of the 1048 children with goiter at the first examination who did not take iodine, only 145 decreased in size.

ADENOMA

A certain number of goiters are nodular and are therefore, but perhaps erroneously, considered adenomatous A few of these nodules have the structure of fetal thyroid and are assumed to arise from embryonal cell nests, but the great majority of them seem to be encapsulated masses of adult thyroid tissue. Many observers believe these nodules to represent areas of disorderly growth in response to some unknown stimulus, and that a state of hyperthyroidism can be initiated from such a nodule without diffuse involvement of the gland. However, the studies of Rienhoff, confirmed by both Dunhill and Hertzler, have considerably influenced opinion—studies in which it was shown that the involutional changes occurring in the thyroid glands of patients with exophthalmic goiter who were undergoing remission revealed striking similarities to the histologic picture seen in nodular goiter; Cole and Womack made the same observation in their experimental production of nodular goiter in dogs. This would make of these nodules neoplasms in no sense of the word but involutional bodies whose number and size depend upon the number of remissions and exacerbations in the gland The fact that cases of so-called "toxic adenoma" sometimes develop may simply mean that the diagnosis of toxic adenoma is made during a particularly fulminating exacerbation in a gland that has undergone many milder exacerbations and remissions. The fact that exophthalmos is unusual in these cases need not set them apart as a separate type of thyrotoxicosis for most of the cases develop after the middle thirties, at which time this symptom is also unusual in the nonnodular cases.

THERAPY

The most recent voices to be heard in favor of the surgical removal of all nodular goiters are those of Hinton and Lord (1945), who believed that all non-toxic nodular goiters should be removed surgically because of the high incidence of unsuspected cancer, in reviewing their own experience they found that in 184 cases of clinically benign nodular goiters there was an incidence of 7.6 per cent of cancer on pathologic examination, a figure in close agreement with that of earlier reporters They also made the point that toxic nodular goiters should be removed surgically and should not be treated with the thiouracil preparations. This is certainly the position taken by the vast majority of surgeons but by no means all internists are willing to adopt it. The controversy has been going on for many years, and I certainly have no nuggets of wisdom to contribute towards its settlement, perhaps it is permissible to remark, however that "good" scars and practically no mortality result from the ministrations of the surgeons nowadays and that there are those who feel we should leave them *something* to do in the thyroid field.

THYROTOXICOSIS

(*Exophthalmic Goiter, Graves' Disease, Basedow's Disease*)

Thyrotoxicosis is the name given to a peculiar complex of symptoms of which the chief are enlargement of the thyroid gland, an increase in the basal metabolic rate, a decrease in weight and strength, a characteristic nervous syndrome, exophthalmos usually, and a tendency to gastro-intestinal crises of nausea and vomiting There is often a state of hypermotility of the gastro-intestinal tract, the degree of which, however, is no index of the severity of the disease The classic description of the disease is that of Caleb Parry, in 1786, though the paper of Graves, in 1835, was the first to attract wide attention; Basedow described it again in 1840 Thyrotoxicosis occurs far more often in women than in men and principally between the ages of fifteen and thirty-five, no race being entirely exempt The disease is believed to be of relative infrequent occurrence throughout the world, but doubtless many mild cases are constantly being mistaken for neurasthenia, psychoneurosis and cardiac disorders unrelated to thyrotoxicosis The belief that thyrotoxicosis is more frequent in large cities than in rural districts is not supported by authoritative statistical studies; likewise, the opinion that

even with the development of a pronounced psychosis, muscular tremor,

heavier burden on both the patient and the doctor than in surgically handled cases. He furthermore said that persistences and remissions following surgery amount to not more than 5 per cent, which is much lower than in the cases in which drug therapy alone is used. The incidence of tetanies and vocal cord paralyses, transient or permanent, following operation, he placed at not much over 1 per cent each at the hands of expert thyroid surgeons.

Obviously, therefore, the introduction of thiouracil, and more especially the newer and safer propylthiouracil, has made it possible for the surgeons to achieve results in thyrotoxicosis that were undreamed of a few years ago and one must hesitate long nowadays before declaring that surgery is not the method of choice for the treatment of thyrotoxicosis; particularly is this true since it seems predictable that the use of the propylthiouracil-iodine combination will almost completely eliminate multiple-stage operations and reduce the surgery of patients with hyperthyroidism practically to that of the technical procedure of subtotal thyroidectomy.

Propylthiouracil Therapy without Surgery.—In the seventy-five patients whose symptoms were brought fully under control by the use of propylthiouracil by McGavack *et al.* (1947), the time necessary to bring about complete control in patients who had not previously received thiouracil varied from two to seven weeks. Beierwaltes and Sturgis (1947) found that an initial period of bed rest coupled with the administration of propylthiouracil is accompanied by a greater favorable initial response than is treatment in the ambulatory state although the end result appears to be the same. They found that the average rate of response of the basal metabolic rate in their patients was less than a 1 per cent fall every two days, though a fall twice this great had been reported previously by others. Their experience indicated that 150 mg. of propylthiouracil daily is an adequate dosage for most thyrotoxic patients In their initial study, Astwood and Vander Laan (1946) had found 150 mg. satisfactory both as initial and as continuation dosage until all manifestations of thyrotoxicosis have disappeared. Incidental to the study of this compound by Astwood and Vander Laan it was found that the progress of the hyperthyroidism and the effects of treatment could be as well observed by the use of clinical criteria as by the frequent determination of the basal metabolic rate or the use of other special laboratory procedures. It was felt that the dose could be properly adjusted on the basis of symptoms and such simple signs as the general appearance and behavior of the patient, body weight, pulse rate, forcefulness of the heart beat, condition of the skin, steadiness of the hands, and size and vascularity of the thyroid gland Excessive dosage was suggested by lethargy, excessive gain in weight, pasty and puffy appearance to the face, and conspicuous enlargement of the thyroid gland Williams *et al.* (1947) said they felt that the employment of propylthiouracil would likely be a very satisfactory way of treating the majority of patients because their experience with thiouracil itself had been highly satisfactory. Of their 111 patients who had been treated with thiouracil and had a cessation of therapy, at the time of their report fifty-one were in remissions that had lasted for from three to thirty-one months, forty-four had been free of thyrotoxicosis for more than a year after cessation of therapy, and thirty-three had remained well for more than eighteen months. Of all the patients who remained well without treatment for more than a year only one had a relapse. And following the cessation of treatment most of the patients who had a relapse had it within a few months, 70 per cent within

two months and 88 per cent within five months. In the experience of these observers, factors favoring persistence of remissions were female sex, small goiter, and a mild degree of thyrotoxicosis, age, duration of the disease and nodularity of the gland were not found to exert a significant influence, but it was recognized that these factors might prove important when more experience with drugs of this type has been had. Beierwaltes and Sturgis (1946) had earlier concluded from their experience that 45 per cent of all patients with thyrotoxicosis of the type observed in a large general hospital in the Middle West could be treated with some degree of success with thio-

satisfactory as those of subtotal thyroidectomy, the majority of patients with thyrotoxicosis must still be treated by surgical means; it seems to me not unfair to add, however, that the employment of propylthiouracil, not available at the time of their study, would probably have increased the size of their figure somewhat through elimination of some of the patients turned over to surgery

McGavack *et al.* (1947)

replace operative interf

sure symptoms occur or unsightliness at the neck makes elective surgery

mptoms to recur following

percentage of cases if at-

After the patient has been receiving propylthiouracil for three months or more, it is their practice to decrease the dose by 25 mg. daily and then at each succeeding monthly visit to make a similar deduction until the patient has been maintained for one month on a single tablet of 25 mg. daily. Then, for an additional month, 25 mg is administered every other day If at the end of that time

than this the dose is accordingly reduced to restore the thyroid status to

the therapy It was felt possible that two episodes of urticarial eruption were manifestations of drug sensitivity, and the authors felt that an occasional reaction of this sort was to be expected when the drug came to be extensively

and one other had had febrile reactions accompanied by an extensive skin rash following the use of thiobarbital. In none of these six patients were any untoward effects observed following the use of propylthiouracil Reveno (1947) also reported five patients who were able to take propylthiouracil though thiouracil itself was toxic for them; however, in one of his fifty-four propylthiouracil-treated patients a typical drug fever developed. The only toxic reactions observed in Beierwaltes and Sturgis' (1947) nine months' use of propylthiouracil in forty-two patients were (a) drowsiness during the first two weeks of administration in about 30 per cent of the patients, and (b) acneform dermatitis of the face in one patient, this lesion disappearing when the dosage of the drug was reduced by 50 mg. per day. A skin reaction was also seen in one of Wilson and Goodwin's (1947) patients after seven weeks of therapy. In their seventy-five patients, McGavack *et al* (1947) encountered but one reaction, this occurring in a forty-eight year old woman with a so-called post-menopausal type of toxic nodular goiter, on the seventh day after beginning treatment with propylthiouracil this patient experienced a generalized rash and fever, a picture on the whole closely resembling that seen when she had been previously treated with thiouracil although less marked in degree. Lahey (1947) said he had observed what he called "significant" blood changes in five of 370 patients treated with propylthiouracil and that in one of these instances there occurred a typical severe case of agranulocytosis in which he felt that fatality had been prevented only by the energetic use of penicillin. He also made a point of the fact that the danger of development of sensitivity from repeated courses of treatment with propylthiouracil, should a relapse develop, needs further evaluation as does the possible danger of grave histopathologic changes following prolonged maintenance treatment

At the time of this present writing there are certainly not enough data at hand to answer the question whether propylthiouracil may be safely employed in the treatment of thyrotoxicosis in pregnancy but there are some indications that one should at least proceed with great caution in the employment of the drug in these cases. Reveno's (1946) review of the small series of reported cases in which thiouracil had been employed in the treatment of individuals having diabetes mellitus complicated by hyperthyroidism disclosed that both successes and failures have been had with this prede- [illegible]

[illegible] those who are studying the employ- [illegible] nent of thyrotoxicosis that it will be more effective and less injurious to neighboring tissues than roentgen rays [illegible] without for the reason that the thyroid gland specifically collects [illegible] ion directly within [illegible] s (1946) and Hertz [illegible] may be effectively induced in hyperthyroidism by the employment of this new agent, but it seems [illegible] must of necessity still remain for a considerable [illegible] nt we do not know [illegible] toward side effects or whether cancer may not even be induced The effect of the excretion of radioactive material on the cells of the kidneys is also not known with the exactitude that would be desirable Keating (1947) made two very pertinent points: (a) that the handling of radioactive iodine requires the same kind of

precautions against the insidious and disastrous consequences of radiation for the patient and the technician as does the use of radium or roentgen rays, and (b) that we still require much more information concerning minimal quantities capable of producing radiation effects both on the thyroid gland and other organs

X-Ray Therapy.—Rose (1947) said that the experience of himself and his associates over the past twenty years in the treatment of about 800 cases of hyperthyroidism by x-ray yielded an incidence of satisfactory results amounting to approximately 85 per cent, he said that while the great majority of these patients had been selected for treatment because of the absence of severe visceral complications, larger nodular goiters or an intense degree of toxicity, the results left no doubt in his mind that the favorable responses were far more frequent than could be explained by spontaneous coincidental remission. He said that at the present time he employs x-ray treatment in the following

in such patients to employ irradiation of the pituitary and sometimes of the orbital structures along with moderate amounts of irradiation to the thyroid; (c) a small group of patients who refuse both antithyroid drug therapy and thyroidectomy Rose also said

opinion, expressed a number of

ful trial of roentgen therapy

Soley and Stone (1942) obtained marked improvement or complete relief in thirty-three of their forty-three adult patients, and Dr Soley kindly informed me in early 1947 that in a ten-year follow-up of this group the results were found to be better than at the time of the original publication However, Linnell *et al* (1946) stated that a former member of their group had found that of 140 adults "cured" by roentgen therapy no fewer than 118 were found subsequently to have established auricular fibrillation

neither confirmation nor refutation of the idea Mild reactions, characterized

tinic acid (niacin) or thiamine for a few days before irradiation. Rose and Wolferth's (1941) three cases of mediastinocardiac reaction are unique in the

tracheitis and esophagitis that sometimes occur

Vitamins and Minerals.—Studies in recent years are pointing to the advisability of using supplementary vitamins in these patients. Womack, reviewing the matter in 1940, felt the chief indications to be for vitamins A and B. That

would mean a fish liver oil or carotene to provide vitamin A, thiamine for B, and dried brewers' yeast or at least nicotinic acid (niacin) and riboflavin for the B_2 complex. Williams *et al.* (1943) found that in a majority of forty unselected thyrotoxic subjects, the level of thiamine in the blood was below normal and the administration of thiamine was distinctly advantageous as adjunctive therapy The studies of Puppel *et al.* (1945) indicated to them that ordinarily hyperthyroid patients require at least twice the optimal calcium and phosphorus daily intake of normal individuals. They found milk an excel-

instances in which the proper amount of milk cannot be tolerated, in patients who have been in a severely toxic condition for some time before coming to the physician, and in those with obvious osteoporosis.

Treatment of Thyroid Crisis.—By the term "crisis" is meant severe exacerbation of all the symptoms of thyrotoxicosis. The metabolism, fever and pulse rate rise very high, nausea, vomiting, and often diarrhea are present, and

tative; that is, to submit patients with hyperthyroidism to surgery early before such a severe state can occur. The next best treatment of this condition is to recognize the earliest signs of its possible appearance and to introduce intravenously 40 to 60 drops of 5 per cent glucose and fluids per minute constantly day and night, together with the frequent intravenous administration of 50 per cent glucose, the patient having from 500 to 800 grams of glucose in the twenty-four hours. This is best introduced into the saphenous vein just

Of course in many instances the patient is able to cooperate to some ex- and even to retain some fluid swallowed, in such cases it may suffice to give the iodine by mouth, giving as much as 100 to 200 cc of Lugol's solution in the first twenty-four hours But in any case get large amounts of readily assimilable carbohydrate into these patients, and don't forget the vitamins!

Hyperthermia must often be combated also. Means ... ally cold packs or sponging do not suffice; the ice pack or ice bath has to be used. However, since ice causes vasoconstriction of cutaneous vessels and reduces the loss of body heat by radiation, Crile (1942) thought it more physiological to increase the loss of body heat by evaporation; to this end he described the use of huge amounts of fluid in order to increase perspiration,

using as much as 5000 to 6000 cc. of fluid per day intravenously unless otherwise contraindicated. He also found aspirin very helpful in controlling the hyperthermia.

Treatment of Cardiac Complications.—In some instances of congestive failure and auricular fibrillation in thyrotoxicosis only operation will restore compensation, but in other cases digitalis will be slowly helpful. In the treatment of the tachycardia that is a distinguishing feature of the disease, and for the relief of palpitation that so often distresses the patient, digitalis is useless. Some men find quinidine, or one of the quinine salts, helpful in a dose of 2 grains (0.12 gm.) several times daily, but Gold (1944) found neither of these agents of value.

ADDISON'S DISEASE

This disease, of which only about 300 to 400 cases are annually reported in the United States, is seen principally in adults in the middle period of life, though Jaudon (1946), reporting a case in a female infant six months of age, said that sixty-two proved cases in children below the age of fifteen years had been recorded in the literature prior to June, 1945. Conn and Matthews (1946) [illegible] ysicians should be on guard for the [illegible] Negro since they believed it to be [illegible] than the number of reported case [illegible] two distinct phases [illegible] acte[illegible] of which are the [illegible] has lost weight, is hypo [illegible] and possibly manifests h [illegible] found to be reduced in s [illegible] brown hyperpigmentatio [illegible] surfaces and often [illegible] clusively, of the genitalia, anus, axillae, n [illegible] cosa. Pigmentation is greatest over bony [illegible] often black freckling of the shoulders and [illegible] *critical phase*. the patient manifests, usually suddenly, the symptoms of suprarenal insuff[illegible] anorexia, nausea, vomiting [illegible] and their asso[illegible] chiefly in the [illegible] being greater [illegible] accompanied by blood conc[illegible] rise of serum potassium and of nitrogenous waste products, and reduction of the total base and carbon dioxide-combining power of the blood.

Siglin (1947), at the Mayo Clinic, listed the following procedures that may be employed in the diagnosis of atypical chron[illegible] (1) the intake of [illegible] of acute adrena[illegible] ministration of [illegible] excretion of electrolytes; (3) sodium chloride is reduced in the diet and potassium is added, determination being made thereafter of the chloride content of urine excreted from the forty-eighth to the fifty-second hour; (4) a so-called water test is performed, the first part of this test consisting in a comparison of the volume of urine passed during the night with the volume of the largest hourly specimen passed in

the course of the next morning after administration of a measured amount of water, and the second part consisting in the solving of the *following equation:*

$$A = \frac{\text{Urea in urine (mg per cent)}}{\text{Urea in plasma (mg. per cent)}} \times \frac{\text{Cl in plasma (mg. per cent)}}{\text{Cl in urine (mg per cent)}} \times \frac{\text{Volume of day urine (cc)}}{\text{Volume of night urine (cc.)}}$$

(5) determination is made of the milligrams of 17-ketosteroids in the twenty-four hour urine specimen. Siglin said that the first of the foregoing procedures is potentially dangerous; the second requires carefully conducted balance studies; the third is the most dependable, practicable diagnostic procedure now available; in the fourth a positive result is suggestive of the presence of Addison's disease whereas a negative result fairly conclusively excludes its presence; and that in the fifth, values of 17-ketosteroids that are suggestive of Addison's disease are less than 1 mg. for females and less than 4 mg. for males.

Addison's disease is due to depression or destruction of one or both of the suprarenal glands. According to Snell (1935), in 80 per cent of cases there is fibrocaseous tuberculosis of the glands (Sodeman, 1939, placed the proportion at 90 per cent, and Thorn, 1944, at only 50 per cent) and in the remaining 20 per cent of cases atrophy of the glands of unknown etiology; very rarely carcinoma, gumma, hemorrhage, infarction, mycosis fungoides, or chronic inflammatory changes with fibrosis of the glands have been associated with the disease in an apparent etiologic role. Snell says that in his experience at the Mayo Clinic about one patient in three has had demonstrable tuberculosis elsewhere in the body and one in four roentgenologically demonstrable suprarenal calcification. According to Kendall's (1935) showing, individuals with this disease die as the result of the development and extension of tuberculosis elsewhere in the body if they do not succumb early to the tuberculous suprarenal involvement. *Moehlig (1947) reported* the interesting case of an Addisonian fatality in a patient whose maternal aunt had died of Addison's disease (verified at autopsy) and whose niece (a brother's daughter) was developing pigmentation; Moehlig therefore felt justified in *postulating an adrenal anlage defect.*

THERAPY

Sodium Chloride and the Low Potassium Diet.—Of the value of a high sodium chloride intake there can be no doubt. The average daily salt intake, which in the United States is probably 6 gm., is often augmented by an additional 6 to 20 gm., taken in enteric-coated tablets. During crises of course large amounts of saline are administered intravenously. Wilder (1937) and his associates at the Mayo Clinic made a valuable contribution in showing that even with the administration of as much sodium as is contained in 18 [illegible] develop unless [illegible] al 4 gm. intake [illegible] low potassium [illegible] as supplements [illegible] and the [illegible] nicotinic [illegible] agents). [illegible], broths, [illegible] eats and [illegible] lumes of [illegible]

vegetables should be cut into small p[illegible] water.

Desoxycorticosterone.—Patients who cannot be reasonably well controlled by the use of sodium chloride and a low potassium diet must be treated with desoxycorticosterone acetate in addition, this agent being a natural steroid of the adrenal cortex which was synthesized by Steiger and Reichstein, in 1937.

Effect.—This agent affects almost exclusively electrolyte and water metabolism. The most noticeable and immediate effect is a gain in weight associated with the retention of sodium chloride and water; indeed, failure to gain weight within forty to seventy hours indicates insufficient dosage. There is a fall in serum potassium to a very low level, kidney function is improved, the patient feels, looks and behaves much better. The blood pressure may

TABLE 13.—LOW POTASSIUM DIET (WILDER ET AL.)
Potassium, 1.6 gm., protein, 57 gm.; calories, 2350

Food	Gm.	Approximate measures.
Breakfast		
Orange juice	100	½ glass
Cornflakes	15	1 serving
Egg	50	1
Bread	50	2 slices
Butter	20	2 squares
Cream, 40 per cent fat	75	¾ cup
Coffee if desired		
Dinner		
Beef tenderloin (weight uncooked)	70	1 average serving
Potato, thrice boiled	100	1 average serving
Carrots	25	1 small serving
Celery	25	2 celery hearts
Grapefruit	55	4 sections
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent fat	20	1 tablespoonful
Tea or coffee if desired		
Supper		
Cheese	40	2 cubic inches
Rice (weight dry)	25	1 average serving
Tomato	60	½ average serving
French dressing	15	1 tablespoonful
Apple	80	¾ average size
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent fat	20	1 tablespoonful
Tea or coffee if desired		

rise very rapidly but it often requires weeks to attain a normal level. As the condition improves the size of the heart increases; indeed McGavack (19[illegible]) proposed the stud[illegible] of heart [illegible]
Co[illegible]
of [illegible]
an[illegible]
th[illegible]
but this product is not commercially available to my knowledge.

Administration.—In 1941, Thorn advocated the maintenance of a daily sodium chloride supplement constant at 5 gm., but by 1944 he had altered his position in view of the fact that some clinicians prefer not to use sodium chlo-

ride in conjunction with desoxycorticosterone at all, the reason being the agent's potency in effecting the retention of sodium and chloride. Thorn says it is now his practice to begin therapy with 2.5 mg. of desoxycorticosterone acetate injected once daily and a 1 gm. tablet of sodoium chloride (enteric coated) three times daily with meals. After the patient has been maintained in good condition on these injections for two or three months, pellets of the crystalline hormone may be implanted subcutaneously, implanting 1 pellet of 125 mg. for each 0.5 mg. of hormone required by daily injection, the pellets usually providing effective therapy for approximately twelve months. Thorn describes the technic of implantation as follows: "The infrascapular region posteriorly is usually selected for pellet implantation. Strict asepsis is observed. The operative field is now prepared with iodine and alcohol and the site of the incision is infiltrated with procaine 1:200 solution. A transverse incision 2 to 4 cm. in length is made a few centimeters below the inferior spine of the scapula. With blunt dissection a number of small pockets, 2 to 3 cm. in depth, are prepared in the subcutaneous tissues. The opening of each pocket is held far enough apart by a nasal dilator to permit pellets to be dropped gently to

many as 10 to 15 pellets through a single incision. Di Maio has recently described a modification of this technique which has the advantage of a smaller incision. A trocar is employed to implant the pellets in a row at some distance from the margin of the incision." Jaudon (1946) implanted four pellets in a child of two years of age. Anderson *et al.* (1940), confirmed by Turnoff and Rowntree (1941), found sublingual therapy satisfactory; the latter's patients

ne glycol under the tongue

tion after fifteen minutes.

sublingual application of

desoxycorticosterone caused swelling of the salivary glands and salivation. Dunlop (1943) found this method effective but very cumbersome and wasteful; he also administered the agent effectively sublabially in tablets, but thought this also a wasteful though convenient method.

Overaction and Precautions—Excessive edema may occur and may be counteracted by reduction in dosage of hormone or sodium chloride, not both simultaneously for fear of provoking crisis. Hypertension seems extremely likely to occur and to be accompanied by signs of serious cardiac overwork; dosage adjustment again is said to handle this situation; Currens and White's (1944) two patients responded well to digitalis Hypoglycemic reactions are

(1945) study suggested that in Addison's disease there is a ... e response of the autonomic nervous system that may contribute to the inability of the treated Addisonian patient to react normally to altered environmental conditions or minor stimuli of many kinds Excessively low serum potassium

in connection with this therapy that Tooke *et al.* (1940)

nt and found

thout danger

if the diet were *not* kept low in potassium; indeed, in some instances it even seemed advisable to supplement a normal diet with some additional potassium in the form of potassium citrate. Wilder (1940) carefully pointed out that this [illegible]

in the cerebral arteries found at autopsy in their patient were due to the administration of desoxycorticosterone in moderate therapeutic dosage over a long period of time since such administration to animals produced similar but not identical lesions.

Cortin and Adrenal Gland Transplantation.—The preparation of the adrenal cortical hormone dates from the work of Rogoff and Stewart, and Hartman independently, in 1927, with subsequent refinements in methods by Hartman, and Swingle and Pfiffner "Cortin" preparations are commercially available, but the dosage is very high, the cost is absolutely prohibitive save for a very few individuals (Thorn, 1944, said that most patients will require 10 to 30 cc. intramuscularly per day at a cost of three dollars to ten dollars), and it has not been demonstrated to the satisfaction of all workers that therapy with these preparations is reliably effective It does not seem to me that the general practitioner is likely to use "cortin," particularly now that desoxycorticosterone is available, except in rare instances in the treatment of a crisis (see below).

Broster and Gardiner-Hill (1946) reported the remarkable grafting into a [illegible]

signs of Addison's disease, that the sodium chloride withdrawal test showed that her blood sodium no longer fell below normal, and that for the fourteen months of observation after the operation she had been able to leave off substitution therapy with sodium chloride without relapse.

Ascorbic Acid (Vitamin C).—There are observations indicating the participation either of vitamin C in cortical function or of cortical function in vitamin C metabolism. The state of our knowledge is still inexact but it would seem unlikely that any harm could be done, and possibly some good might accrue, from supplementing the dietary with additional ascorbic acid (see Scurvy for methods).

Therapy of Crisis.—Thorn (1944) reported the giving of 1000 to 1500 cc. of physiologic saline solution with 5 to 10 per cent of dextrose, repeating the infusion in six to twelve hours and subsequently at least once daily until the temperature is normal and the patient is taking fluids and eating well. He considered morphine contraindicated and that all unnecessary examinations should be deferred at this period. Twenty-five cubic centimeters of cortin are added to the first intravenous infusion and another 10 cc. are given subcutaneously, repeating the latter at two- to four-hour intervals until fever subsides, [illegible]

saline solution administered, appearance of excessive fluid retention, and [illegible]

made at one- to two-hour intervals day and night. A fall in blood pressure

that seems to be present in almost all living cells. Cori (1946) demonstrated in the body the presence of a specific inhibitor of hexokinase, and it now seems highly likely that the sole function of insulin is to abolish this inhibition. Another interesting development is the discovery that the injection of a substance called alloxan into experimental animals causes necrosis of the isl [illegible]
cations [illegible]
experime [illegible]
however, that this extremely interesting experimental work with alloxan will lead directly to any clinical applications.

The most frequent time of onset is in the early fifties, but the disease may appear at any age. Formerly diabetes in children, in young adults and in pregnant women was felt to have an almost hopeless prognosis, but insulin has entirely changed the status of these patients. The disease is encountered in all races; incidence is higher in Hebrews than in Gentiles and apparently higher too in the Irish, it occurs more often in the rich than in the poor. The hereditary transmission of a "tendency" for development of diabetes, as well as the contention that obesity and probably also thyrotoxicosis predispose, may tentatively be considered proved; indeed Newburgh and Conn (1939–1942) reported a group of individuals whose glycosuria and hyperglycemia disappeared upon correction of their obesity alone. It is of interest to record the fact that Gendel and Benjamin (1946) reviewed the records of all patients treated for diabetes at one of the general hospitals during the War—a total of forty-four cases in 21,993 admissions—and saw all the patients personally; they concluded that in no case was it possible to prove a direct causal relation between any sort of stress incident to military service and a subsequent development of permanent diabetes, a finding certainly in opposition to the position that psychogenic factors may predispose to the onset of the disease. Despite the fact that the literature is replete with reports of "acute" cases, it is still the consensus that in the majority of instances the onset is gradual. Joslin (1947) said that the present statistics on diabetic mortality are of little value since diabetics really have almost ceased to die of their diabetes although they die with diabetes. He elucidated this statement by saying that formerly 63.8 per cent of his patients died of coma and these deaths were rightly ascribed to diabetes, whereas today about 3 per cent die of coma which leaves some 61 per cent of deaths due to other reasons; to fill this statistical gap cancer has jumped from 1.5 to 8 9 per cent and arteriosclerosis in its various forms from 17.5 to 67.4 per cent—he said that obviously these conditions are not diabetic deaths and so they elude the statistician. Joslin has also said, however, that diabetics do not live as long as non-diabetics and that in fact the life expectancy of his diabetic patients is only about two-thirds that of non-diabetic patients, he felt that Robbins and Tucker (who, in 1944, had found in an analysis of 307 autopsies on diabetic patients at the Boston City Hospital that the diabetic lives as long as the non-diabetic nowadays but that there are certain hazards that he is seemingly more likely to encounter, namely, coronary occlusion, peripheral vascular disease, infections of the extremities and acute pyelonephritis) had probably overlooked the fact that the usual figures for the expectation of life relate to the expectation at birth and that in referring to the expectation of life for diabetic patients one should take account of the age in which the diagnosis of diabetes was first made. The frequency with

especially in America It does not seem that even the best type of treatment to date has been able to lower the incidence of retinitis in diabetics Marks (1947), in an authoritative statistical analysis, said that the known diabetics in the United States number about 700,000 and that the annual number of new cases is at least 55,000, he also estimated that 2.1 per cent of the males and 3 8 per cent of the females in our present population will eventually become diabetic. He stated that the death rate in the United States is the highest in the world, that within the country the rates are highest in the North and lowest in the South and Southwest, and that in most States the rate in the white population is lower than in the non-white population.

Attempts to classify cases of diabetes as mild, moderate, or severe upon the degree of any of the symptoms, and especially with regard to the amount of sugar in the urine or in the blood at the first examination, are usually unsuccessful for two reasons. first, because the patient often presents himself either after a food debauch, and consequently with a high glycosuria, or after a period of severe abstinence designed to impress the new physician with his earnestness as a patient, and second, because it is by no means infrequent for patients with an astonishingly low carbohydrate tolerance to respond remarkably well to treatment that is properly planned and executed. That most cases of diabetes are actually mild is a truth that is becoming increasingly apparent—which is, however, by no means the same thing as saying that the disease is not a serious one even in the mildest cases

In the Sanskrit manuscript of Suśruta (fifth century, A D) the principal symptoms of this disease are noted and the entity is given a name that translates into "honey urine." The observations were several times confirmed by Christian and Mohammedan writers of the medieval period, but it was only in 1776 that Matthew Dobson proved that the sweetness of blood and urine was actually due to the presence of sugar.

THE DIETETIC PROBLEM IN DIABETES TREATMENT

[illegible]

made up to a very great extent by increasing the amount of protein in the [illegible]

[illegible]

they are unable to use. As compared with protein, fat has three advantages:

first, each gram yields 9 rather than 4 calories; second, its specific dynamic action is lower than that of protein, thus enabling it to be used without so greatly increasing the total caloric need; and third, only 10 per cent of it is converted into carbohydrate in the course of catabolism. But its disadvantages are unfortunately grave. Of the two disadvantages of fat the least important, but by no means *un*important, one is the fact that fat, in large enough amount to raise the total calories to a point approaching satisfaction, is very repugnant to the gastro-intestinal tract and often provokes a most undesirable state of indigestion. But the chief disadvantage is that fat is improperly metabolized in diabetes. We used to believe that this was because fat needs carbohydrate for its proper oxidation, but now the work of Stadie (1940) and others has made that position untenable; however, though it is no longer permissible to say that "fat burns in the fire of carbohydrate," we do know that beyond a certain level in the diabetic fat metabolism is incomplete and that part of the fat catabolized is excreted in the form of ketone bodies. These ketone bodies are poisonous in that they attach themselves to basic radicals from which they displace the weaker carbonic acid, thus bringing about the presence of carbon dioxide in excess in the blood. If this goes on in only a small way, surplus carbon dioxide is eliminated through the lungs and some of the ketone bodies are passed out through the kidneys, but if protein is being kept as high as is

dilemma were grasped firmly, if ineffectually, by simply starving the patient. If his carbohydrate tolerance was very low and he could not bear large amounts of protein and fat for the reasons just presented, he was merely placed on that

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scene its use was at first merely engrafted upon the above treatment, *i.e.*, the "tolerance" of the patient was determined by building up the carbohydrate after starvation to the amount he could utilize and then insulin was added to enable him to take a little carbohydrate for a little more comfort. In those days the apportioning of the carbohydrate (C), protein (P), and fat (F) fractions of the diet was dictated by the formula $F = 2C + \frac{1}{2}P$, by which Woodyatt had made clinically available the laboratory researches of Shaffer. But as time went on and experience increased, the following clinical observations made it apparent that the principle needed considerable revision: (1) Patients so strictly managed were always perilously close to ketosis and therefore at all times in a more or less potentially dangerous condition (2) Patients who did not take the thing too seriously and now and then moderately indulged in excess carbohydrate often escaped acetonuria despite the development of glycosuria. (3) With a little sugar in the urine the patient usually felt better. (4) By utilizing to the

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drates and low in fats, under which regimen it is found that insulin

astonishingly larger amounts of carbohydrate than was thought possible in an earlier period. These high carbohydrate-low fat diets are more palatable, they are cheaper and easier to prepare, they are more nearly normal, and they maintain the patient in a stronger condition—a stoker or plowman *can* stoke or plow —and feeling thoroughly at ease. Insulin reactions are fewer and less severe. It has also been remarked that upon the new type of therapy patients who formerly had persistently high blood sugars are seen less frequently and that the refractory diabetic responds more "normally." It has not been conclusively shown, however, that the new diets are effective in lowering the incidence of arteriosclerosis.

BARACH'S SIMPLE METHOD OF DIETARY COMPUTATION

(*The Tables will be found immediately following the discussion of them below.*)

Diabetic Table A.—This provides maintenance diets for males and is based upon the maximum longevity tables of the Metropolitan Statistical Bureau. It takes into account the patient's height, his body build and the extent to which he is physically active. The protein portion of the diet varies between 0.75 and 1.0 gm per kilo in round numbers. The total fat allowance is determined by the very important fact that the dietitian cannot make up a satis- [illegible]

[illegible]

the daily allowances. If there is acetone and diacetic acid *without* glycosuria, too little carbohydrate is being given, and both additional carbohydrate and insulin are necessary. Barach (1947), reviewing a series of about 2000 cases, found that almost 100 per cent of the children in this series required insulin, that at middle age approximately 60 per cent of patients required it, and that in elderly diabetics only about 35 per cent required it. If there is acetone and diacetic acid *with* glycosuria, fat and protein must be reduced and carbohydrate and insulin are imperatively needed.

It will be observed that in employing this table it is not necessary to do any [illegible]

last diet prescribed.

Diabetic Table B.—This is the same as Table A except that it takes into account the somewhat different weights and nutritional requirements of women.

Diabetic Table C.—This provides maintenance diets for growing children. It takes into account the differences in weight between girls and boys and the [illegible]

Diabetic Table A.—Maintenance Diets for Men, Aged 25 and Over (Barach)

HEIGHT WITH SHOES		BODY FRAM	IDEAL		N U	CALORIC REQUIREMENT				N U	CALORIC REQUIREMENT				N U	CALORIC REQUIREMENT			
Ft.	In	Bulk																	
5	2	Small	120	55	1	1375	130	55	70	2	1515	150	50	80	3	1650	170	60	80
5	2	Med	128	58	4	1450	150	55	70	5	1595	160	60	80	6	1740	180	65	85
5	2	Large	137	62 5	7	1560	150	60	80	8	1725	175	65	85	9	1875	195	70	90
5	3	Small	123	56	10	1400	140	55	70	11	1540	150	55	80	12	1680	175	65	80
5	3	Med	131	59 5	13	1480	140	50	80	14	1635	170	60	80	15	1785	175	70	90
5	3	Large	133	63	16	1575	155	60	80	17	1725	175	65	85	18	1890	200	70	90
5	4	Small	127	58	19	1450	150	55	70	20	1595	160	60	80	21	1740	180	65	85
5	4	Med	135	61 5	22	1540	150	55	80	23	1690	175	65	80	24	1845	195	65	90
5	4	Large	143	65	25	1625	170	55	80	26	1790	175	70	90	27	1950	210	75	90
5	5	Small	131	59 5	28	1480	140	50	80	29	1635	165	60	80	30	1785	175	70	90

Diabetic Table B.—Maintenance Diets for Women, Age 25 and Over (Barach)

HEIGHT WITH	BODY	IDEAL	N	CALORIC REQUIREMENT	N	CALORIC REQUIREMENT	N	CALORIC REQUIREMENT

240 gm. of carbohydrate, 80 gm. of protein and 95 gm. of fat daily. One then turns to this present Table D and finds, in the column designated by the check mark (√), that the patient may take 365 gm of 6 per cent fruit, 40 gm. of cereal (dry weight) and 60 gm. of white bread for breakfast; 190 gm. 20 per cent vegetable, 200 gm. 6 per cent fruit and 60 gm. bread for lunch; 180 gm. 20 per cent vegetable, 200 gm. 6 per cent vegetable, 200 gm. 6 per cent fruit and 40 gm. bread for dinner in the evening. In obtaining the carbohydrate

DIABETIC TABLE C —MAINTENANCE DIET FOR DIABETIC CHILDREN (BARACH)

Age Weight.			Minimum Diet. Daily Allowance.				Maximum Diet. Daily Allowance.			
Yrs.	Lbs	Kilos	Calories Per Day.	Carbo-hydrate Grams	Protein Grams	Fat Grams	Calories Per Day.	Carbo-hydrate Grams.	Protein Grams.	Fat Grams
½	15	7	600	75	25	25	700	90	30	25
1	20	9	800	100	30	30	1000	125	40	35
2	26	10	880	110	35	35	1100	140	45	40
3	31	14	960	120	40	40	1200	150	50	45
4	35	16	1040	130	40	40	1300	165	50	50
5	38	17	1120	140	45	45	1400	175	55	55
6	43	19	1200	150	45	50	1500	185	55	60
7	50	22	1280	160	50	50	1600	200	65	60
8	55	25	1360	170	55	50	1700	215	65	65
9	61	28	1440	180	55	55	1800	225	70	70
10	67	30	1520	190	55	60	1900	235	70	75
11	75	34	1600	200	65	60	2000	250	70	80
12	81	37	1680	210	65	65	2100	265	80	80
13	90	40	1760	220	65	70	2200	275	85	85
14	103	47	1840	230	70	70	2300	285	85	90
15	112	50	1920	235	75	75	2400	300	90	95
16	126	57	2000	240	80	80	2500	315	95	95
17	133	60	2080	240	80	90	2600	325	100	100
18	138	63	2160	240	85	95	2700	340	100	105
19	138	63	2240	245	90	100	2800	350	100	110
20	139	63	2320	240	95	110	2900	365	100	115

... below Maximum. This diet may be increased

... fat

... be

... ram

portion she will also have obtained 20 gm. protein (the lowest figure in the 240 gm. column); this is to be taken account of in the use of the next table.

... the protein and fat portions of the diet.

... of protein,

... protein were

incidentally obtained, the ... allows the patient 60 gm. of protein, which, as designated by the check mark (√) in this

DIABETIC TABLE D.—CARBOHYDRATE PORTION OF ALLOWANCE (BARACH)

	Carbohydrate	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
	Food.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
Breakfast	6 per cent fruit	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	135	200	235	300	355	400	400	400	400	400	400
	Cereal (dry weight)	14	20	25	28	34	23	23	34	37	23	34	40	28	34	37	40	40	40	40	40	40	40	40	40	40	40
	Bread						20	20	20	20	40	40	40	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Lunch	20 per cent vegetable	50	50	60	70	90	60	70	90	110	120	140	150	170	190	180	170	190	200	170	190	200	225	225	225	225	225
	6 per cent fruit	113	135	135	200	200	200	200	200	200	200	200	200	200	200	200	200	200	235	200	200	235	235	300	300	300	300
	Bread						20	20	20	20	20	20	20	20	20	40	40	40	40	60	60	60	60	60	60	60	60
Dinner	20 per cent vegetable	50	50	50	50	50	50	70	80	100	120	130	150	170	180	150	170	180	150	170	180	200	225	225	245	245	280
	6 per cent vegetable	60	80	100	100	135	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	300	300	300	300
	6 per cent fruit	60	65	130	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	300	300	350
	Bread															20	20	20	40	40	40	40	40	40	40	50	50
	Grams protein incidentally obtained, and therefore to be subtracted from Protein-Fat Portion			5	6	5	5	5	10	10	10	10	10	10	10	15	15	15	15	20	20	20	20	22	22	23	25

present table, will permit her to have 100 gm. of meat for each of the three meals. It will be noted that in taking this 60 gm. of protein she also acquires incidentally 60 gm. of fat; this fact will be taken account of in the next table.

Diabetic Table F.—This table provides the additional fat portion of the diet. Our supposititious patient is to have 95 gm. of fat, but in acquiring her protein she also acquired 60 gm. of fat incidentally; one therefore subtracts 60 from 95 and allows her 35 gm. of fat, which, as indicated by the check mark (√) in this present table, will permit the taking of 12 gm. of butter at breakfast, 14 gm. of butter or mayonnaise for lunch and 15 gm. of butter or mayonnaise for dinner—in short, this additional fat portion is to be distributed more or less equally between the three meals.

DIABETIC TABLE E.—PROTEIN AND FAT PORTION OF THE ALLOWANCE (BARACH)

	Protein.	15	20	25	30	35	40	45	50	55	60 ✓	65	70	75	80	85	90
	Fat (incidental)	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Break-fast	Grams meat	25	30	40	50	55	65	75	80	90	100	105	115	125	130	140	150
Lunch	Grams meat	25	35	40	50	60	70	75	85	90	100	110	115	125	135	140	150
Dinner	Grams meat	25	35	45	50	60	70	75	85	95	100	110	120	125	135	145	150

DIABETIC TABLE F.—ADDITIONAL FAT PORTION OF THE ALLOWANCE (BARACH)

	Additional fat	10	15	20	25	30	35 ✓	40	45	50	55	60	65	70	75	80	85
Break-fast	Butter	4	6	7	10	12	12	15	17	19	21	23	22	22	23	22	22
	Fat, salad or olive oil																
Lunch	Butter or mayonnaise	4	6	8	10	12	14	15	17	19	21	23	22	22	22	23	22
	Fat, salad or olive oil												3	2	8	12	14
Dinner	Butter or mayonnaise	4	6	8	10	12	15	17	19	21	23	25	24	24	24	24	24
	Fat, salad or olive oil						.					3	5	10	10	14	18

Diabetic Table G.—This lists carbohydrate exchanges that provide consider- ... the table is very easily

... l vege-

tables.

Diabetic Table I.—This is a table of meat exchanges and, as in the case of the carbohydrate table, is very easily employed by following the simple instructions.

Diabetic Table J.—This is simply a table of supplementary information on foods, designed to supply the answer to numerous frequently asked questions.

DIABETIC TABLE G —CARBOHYDRATE EXCHANGES (Continued) —

Instructions —If you wish to have the patient *trade* some of his fruit or vegetables for milk, cream, bread and butter, *or* cereal and butter, proceed as follows find the *quantity of the new* food and then omit the quantity of fruit or vegetables *appearing* in the same column For example choosing to allow a glass of milk (8 ounces or 240 cc), find the 240 milk column and then omit the 12 gm carbohydrate there stated, either by leaving off *400* gm *of 3 per cent fruit* or vegetable, or 200 gm of 6 per cent, or 80 gm *of 15 per cent*, or 60 gm of 20 per cent To even things up completely *in* this instance, however, 36 gm. of meat must also be omitted, *as shown*

Grams Carbohydrate	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
3% Vegetable	85	100	135	165	200	235	265	300	335	365	400	435	465	500	535	565	600											
6% Fruit or Vegetable	35	50	85	85	100	115	135	150	165	185	200	215	235	250	265	285	300	335	365	400	435	465	500	535	565	600		
15% Fruit or Vegetable	15	20	25	35	40	50	55	60	65	75	80	85	90	100	105	115	120	135	145	160	175	190	200	210	225	240	255	265
20% Fruit or Vegetable	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	100	110	120	130	140	150	160	170	180	190	200
Take Grams Milk	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360	400										
Leaving off Grams Carb.	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20										
and Grams Meat	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	60										
Take Grams Cream	40	80	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360	400										
Leaving off Grams Carb.	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20										
and Grams Meat	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	60										
and Grams Butter	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	80										
Take Bread + Butter									20 +0	22 +0	24 +0	26 +0	28 +0	30 +5	32 +5	34 +5	36 +5	40 +5	44 +5	48 +6	52 +6	56 +7	60 +7	64 +8	68 +8	72 +9	76 +9	80 +10
Leaving off Grams Carb.									10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
and Grams Meat									10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
Take Cereal + Butter									14 +0	16 +0	18 +5	19 +5	20 +5	21 +5	23 +5	25 +5	26 +5	28 +5	32 +6	34 +6	37 +7	40 +8	43 +8	45 +8	48 +9	52 +9	54 +10	57 +10
Leaving off Grams Carb									10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
and Grams Meat									10	12	14	14	15	17	18	19	20	21	22	25	28	30	31	32	34	36	38	40

Diabetic Table II.—Percentage Vegetables and Fruits

3 per cent (sometimes called 5 per cent)

Vegetables (fresh)

Artichokes (French, as used for salad)	Celery	Mustard greens	Summer squash
Asparagus	Cucumbers	Okra	Swiss chard
Beans, green or wax (or canned)	Eggplant	Pickles (sour)	Tomatoes
Beet greens	Endive	*Radishes*	Watercress
Broccoli	Green peppers	Rhubarb	
Brussels sprouts	Leeks	Sorrel	
Cabbage	Lettuce	Sauerkraut (or canned)	
Cauliflower	Marrow	Spinach	

6 per cent (sometimes called 10 per cent)

Vegetables		*Fruits*	
Beets	Oyster plant	Avocado	Muskmelons, cantaloupe, honeydew
Carrots	Pumpkin	Blackberries	Oranges
Dandelion greens	Rutabaga	Cranberries	Peaches
Kale	String beans	Gooseberries	Pineapple
Kohlrabi	Squash	Grapefruit	Strawberries
Onions	Turnips	Lemons	Tangerines
		Limes	Watermelon

15 per cent

Vegetables		*Fruits*	
Artichokes (Jerusalem, or "ground," fresh; when cut into chips and dried, reckon the C value per gm. doubled)	Green peas	Apples	Huckleberries
	Lima beans (canned)	Apricots	Nectarines
	Parsnips	Blueberries	Papaws
	Salsify	Cherries	Pears
	Yams	Currants	Plums
		Grapes	Quinces
		Guavas	Raspberries

20 per cent or higher

Vegetables		*Fruits*
Baked beans	Potatoes (baked or boiled)	Bananas
Shelled beans	White	Figs (fresh)
Green corn	Sweet	Prunes

Diabetic Table I.—Meat Exchanges (Barach)

Instructions—If your patient wishes to trade about among the meats, or to substitute fish, cheese, or eggs for some of his meat allowance, this can be easily arranged for him. For example, suppose his protein allowance has been stated in Table G as 100 gm. meat for dinner. Let us say he has been taking this in the form of 70 gm. chicken or turkey plus 8 gm butter, as shown in the Table (below) in the 100 gm. meat column, but that, like a chap I know, he would prefer a tasty bit of American cheese, *you need* then only have him omit his 70 gm. of chicken or turkey, and the 8 gm butter which go with it, and take on 69 gm. American cheese, dropping at the same time another 6 gm of butter

(a) EAT	25	30	35	40	45	50	55	60	65	70	75	80	85
MB	25 +2	30 +3	35 +3	40 +4	45 +4	50 +4	55 +4	60 +4	65 +5	70 +5	75 +6	80 +6	85 +7
AK	18 +4	21 +4	25 +5	28 +6	32 +7	36 +8	39 +8	43 +9	47 +10	50 +11	54 +12	56 +13	61 +14
AK	20 +4	25 +4	29 +5	33 +5	37 +6	42 +7	46 +7	50 +8	54 +9	58 +9	62 +10	66 +11	70 +12
URKEY	18 +2	20 +2	24 +2	28 +3	31 +3	35 +4	38 +4	42 +4	45 +4	48 +5	52 +5	56 +6	60 +6
EF	16 +4	20 +5	24 +6	27 +7	30 +8	34 +9	37 +10	40 +11	43 +12	46 +13	50 +14	53 +15	56 +16
LF	18 +1	22 +1	26 +2	30 +2	34 +2	38 +3	42 +3	46 +3	50 +3	54 +4	57 +4	60 +4	64 +5
PS. EF r	22 −2	25 −2	30 −2	35 −3	40 −3	45 −4	50 −4	55 −4	60 −5	64 −5	68 −5	72 −6	76 −6
raw)	25 +5	30 +6	35 +7	40 +8	45 +9	50 +10	55 +11	60 +12	65 +13	70 +14	75 +15	80 +16	85 +17
led) r	38 −3	46 −3	54 −4	62 −5	70 −6	77 −7	85 −7	92 −8	100 −9	108 −10	115 −10	123 −11	131 −11
M r	22 −1	26 −2	30 −3	35 −3	40 −4	45 −5	50 −5	55 −5	60 −6	64 −6	68 −7	72 −7	76 −8

(a) EAT	90	95	100	105	110	115	120	125	130	135	140	145	150
MB	90 +7	95 +7	100 +8	105 +8	110 +8	115 +9	120 +9	125 +10	130 +10	135 +11	140 +11	145 +12	150 +12
AK	64 +15	68 +16	72 +16	75 +16	78 +17	82 +18	86 +19	90 +20	93 +20	97 +21	100 +22	104 +23	108 +24
AK	74 +13	78 +14	83 +14	88 +15	92 +16	96 +17	100 +18	104 +18	108 +19	112 +20	116 +20	120 +21	124 +21
URKEY	64 +7	67 +7	70 +8	73 +8	76 +9	79 +9	82 +10	86 +10	90 +11	94 +11	97 +12	101 +12	105 +12
EF	59 +17	62 +18	66 +18	69 +19	73 +20	76 +21	80 +22	83 +23	86 +24	89 +25	92 +26	96 +27	100 −28
LF	68 +5	72 +6	76 +6	80 +7	84 +7	86 +7	92 +8	96 +8	100 +8	104 +8	108 +9	112 +9	115 +9
PS. EF r	80 −7	85 −7	90 −7	95 −8	100 −8	104 −8	109 −8	114 −8	118 −9	122 −9	127 −10	131 −10	136 −11
raw)	90 +18	95 +19	100 +20	105 +21	110 +22	115 +23	120 +24	125 +25	130 +26	135 +27	140 +28	145 +29	150 +30
led) r	139 −12	146 −13	154 −14	162 −14	169 −14	177 −15	184 −16	192 −17	200 −18	208 −19	215 −20	223 −21	230 −21
M r	80 −9	85 −10	90 −10	95 −11	100 −11	104 −12	109 −12	114 −12	118 −13	122 −13	127 −14	131 −14	136 −15

DIABETIC TABLE I (*Continued*)

FRESH HAM STEAK minus Butter	15 −2	18 −2	21 −3	24 −3	27 −4	30 −4	33 −5	33 −5	39 −5	42 −6	45 −6	48 −7	51 −7
SPARE RIBS minus Butter	20 −3	24 −3	28 −4	32 −4	36 −5	40 −6	44 −6	48 −7	52 −8	56 −9	60 −10	64 −10	68 −11
FRIED HAM minus Butter				9 −1	14 −2	18 −4	23 −4	28 −4	32 −4	36 −5	40 −5	45 −6	50 −7
and Eggs				1	1	1	1	1	1	1	1	1	1
*BACON (Lean) weigh raw minus *Butter*	34 −10	40 −12	47 −14	54 −16	60 −18	67 −20	73 −22	80 −24	87 −26	94 −28	102 −30	107 −32	113 −34
TUNA FISH, SARDINES (canned) plus Butter	21 +1	26 +1	30 +1	34 +1	39 +1	43 +2	47 +2	51 +2	55 +2	59 +2	63 +3	68 +3	72 +3
SALMON (canned) plus Butter	22 +2	26 +2	30 +3	35 +3	40 +4	45 +5	50 +5	55 +5	60 +6	64 +6	68 +7	72 +7	76 +7
SPANISH MACKEREL plus Butter	20 +4	25 +4	29 +5	33 +6	37 +7	42 +8	46 +9	50 +10	54 +11	58 +12	62 +12	66 +13	70 +13
BLUE FISH plus Butter	18 +5	22 +5	26 +6	30 +7	34 +8	38 +9	42 +9	46 +10	50 +11	54 +12	57 +13	60 +14	64 +15
SALT COD plus Butter	20 +7	24 +8	28 +9	32 +10	36 +11	40 +12	44 +14	48 +15	52 +16	56 +17	60 +18	64 +20	68 +21
SHAD, WHITE FISH HALIBUT, LAKE TROUT plus Butter	Approx Values		24 +2	28 +3	31 +3	35 +4	38 +4	42 +4	45 +4	48 +5	52 +5	56 +6	60 +6
AMERICAN CHEESE minus Butter	16 −1	19 −1	24 −2	27 −2	30 −3	34 −3	37 −3	40 −4	44 −4	48 −4	52 −4	55 −5	59 −5
COTTAGE CHEESE plus Butter	24 +6	30 +8	36 +9	40 +10	44 +11	48 +12	52 +14	57 +15	62 +16	66 +17	71 +18	76 +20	81 +21
EGGS	1	1	1	1	2	2	2	2	2	2	2	3	3

FRESH HAM STEAK minus Butter	54 −7	57 −8	60 −8	63 −8	66 −9	69 −9	72 −10	75 −10	78 −11	81 −11	84 −11	87 −12	90 −12
SPARE RIBS minus Butter	72 −11	76 −12	80 −12	84 −13	88 −13	92 −14	96 −14	100 −15	104 −15	108 −16	112 −16	116 −17	120 −18
FRIED HAM minus Butter	27 −4	32 −5	36 −5	40 −5	45 −6	50 −8	55 −8	60 −9	64 −9	68 −10	72 −10	76 −11	82 −11
and Eggs	2	2	2	2	2	2	2	2	2	2	2	2	2
*BACON (Lean) weigh raw minus *Butter*	120 −36	127 −38	134 −40	140 −42	146 −44	153 −46	160 −48	167 −50	174 −52	180 −54	188 −56	195 −58	201 −60
TUNA FISH, SARDINES (canned) plus Butter	76 +3	80 +3	84 +4	89 +4	93 +4	98 +4	102 +4	106 +5	110 +5	114 +5	118 +5	122 +5	126 +6
SALMON (canned) plus Butter	80 +8	85 +9	90 +10	95 +10	100 +11	104 +10	109 +11	114 +12	118 +13	122 +13	127 +14	131 +14	136 +15
SPANISH MACKEREL plus Butter	74 +14	78 +15	83 +16	88 +16	92 +17	96 +18	100 +19	104 +20	108 +20	112 +21	116 +22	120 +23	124 +24
BLUE FISH plus Butter	68 +16	72 +17	76 +18	80 +19	84 +20	86 +21	92 +22	96 +22	100 +23	104 +24	108 +25	112 +26	115 +27
SALT COD plus Butter	72 +22	76 +23	80 +24	84 +26	88 +27	92 +28	96 +29	100 +30	104 +32	108 +33	112 +34	116 +35	120 +36
SHAD, WHITE FISH HALIBUT, LAKE TROUT plus Butter	64 +7	67 +7	70 +8	73 +8	76 +9	79 +9	82 +10	86 +10	90 +11	94 +11	97 +12	101 +12	105 +12
AMERICAN CHEESE minus Butter	62 −5	66 −6	69 −6	73 −7	76 −7	79 −7	83 −7	86 −7	90 −8	93 −8	97 −8	100 −9	104 −9
COTTAGE CHEESE plus Butter	86 +22	91 +23	96 +24	100 +26	105 +27	109 +28	114 +29	119 +30	124 +32	128 +33	132 +34	137 +35	142 +36
EGGS	3	3	3	3	4	4	4	4	4	4	5	5	5

*Bacon to be broiled until crisp—placed on paper to absorb fat.

DIABETIC TABLE J.—SUPPLEMENTARY INFORMATION ON FOOD

Compound spirit of orange	♏x	0 60
Gluside (saccharin)	gr j	0 06
Alcohol.	℥j	30 00
Water to make	℥iv	120 00

Glycerin.—This substance may also be used in sweetening the food of diabetics in alternation with saccharin.

Seasoning.—Any of the ordinary seasoning agents may be used without reckoning them as food, except that tomato catsup must be employed sparingly

Jerusalem Artichoke.—The bubble of this tuber's superiority was pricked by the studies of Soskin *et al.* (1931), Stein *et al.* (1931), and Campbell (1934), reckon it as any other 15 per cent vegetable

Oysters.—One-half dozen on shell, 4 gm carbohydrate, 6 gm protein, 1 gm fat.

Macaroni (Cooked).—Reckon 1 cupful (200 gm) at 30 gm carbohydrate, 6 gm, protien, 3 gm fat

Crackers.—Twenty gm. of crackers (3 grahams, or 3 sodas, or 5 small saltines) may be reckoned at about 15 gm. carbohydrate, 2 gm protein, 2 gm fat

Mushrooms.—Two hundred gm contain about 1 gm fat, the protein and carbohydrate are largely unassimilable and need not be reckoned with

Nuts.—The assimilable carbohydrate in 50 gm. of almonds may be reckoned at only 2 gm.,

DIABETIC TABLE J—*Continued*

Gelatin—Contains 85 per cent protein, practically no other food constituent, in sweetening, bear in mind that each level teaspoonful of sugar yields 20 gm. carbohydrate.

Ice Cream.—A portion (100 gm) of average commercial ice cream may be reckoned at 20 gm carbohydrate, 4 gm. protein and 14 gm fat.

Milk.—A glass (240 cc.), 12 gm. carbohydrate, 8 gm protein, 10 gm fat.

Butter and Oleomargarine—Ten gm. (a restaurant "square"), 8 5 gm. fat; therefore the purist will frown just a little at an equal exchange of 1 gm butter or margarine for 1 gm oil or fat (see below).

Oils and Fats—Lard, fat, Crisco, olive and salad oils are fat, gm for gm. (see Butter above)

Eggs.—Reckon 1 egg of average size at 6 gm. protein and 6 gm. fat.

Sugar—Sugar is carbohydrate, gm for gm.

Bread—The differences between white, rye, and whole wheat are too slight to be of importance, 1 ordinary slice (½ inch, 30 gm.), 16 gm carbohydrate, 3 gm protein.

THE INSULINS

There are now available four principal forms of insulin and I shall describe the use of each below, but the reader must bear in mind that their insulin value is precisely alike, *i.e.*, a unit of insulin is always just a unit of insulin, no more and no less, whether it is used in the form of regular insulin, crystalline zinc insulin, protamine zinc insulin, or globin zinc insulin. These insulins vary in the rate as which they become absorbed and available in the body, but unit for unit they promote identical degrees of metabolic regulation. The frequently ... dextrose output in the ... ed mathe- ... variables ... as only a crude approximation. One can determine, again roughly, the amount of dextrose in a given specimen of urine from the color reaction obtained upon testing the urine: if the Benedict test solution is used, red corresponds to 4 per cent or more, orange to 2½ to 3 per cent, yellow to 2 per cent, yellow-green to 1 to 2 per cent, gr... orange means 2 per ... cent, green ... consensus w... perfect, simplifies the treatment of the patient enormously.

Insulin is deeply injected subcutaneously, the site being changed so frequently that the same spot is not used more often than once a month. It is well to have patients map out *all available sites in order to avoid duplications.* The sites usually used are the anterior aspects of the legs, the deltoid and triceps regions of the arms, the upper portions of the buttocks and the abdominal wall When, as may occasionally happen, it is necessary to add 0.1 cc. of 2 per cent procaine hydrochloride solution to the insulin, epinephrine should not be used, as is the usual custom with procaine.

... at refrigerator temperature, though as a ... not as ... temper- ... days

... insulins, regular *insulin being the one originally introduced and ...* zinc insulin being the newer preparation relatively free of foreign protein,

require another dose before dinner in the evening, many a dose also before lunch, and in some instances even a fourth injection must be given.

In the day-to-day treatment of diabetes these two insulins are not much

the minority.

Protamine Zinc Insulin.—According to Colwell (1947) the effect of a dose of protamine zinc insulin is demonstrable in about four hours and reaches a prolonged peak in about twenty-four hours, at the end of about three days the effect is exhausted He said that the action of protamine zinc insulin may be considered as that of ordinary insulin stretched out to span about five times as much time with a five-fold loss of intensity at any one time It may be reckoned that the daily administration of 60 units of protamine zinc insulin is roughly comparable to giving about 20 units of ordinary insulin every eight hours

years, says that he has found the two-to-one ratio (2 parts of regular insulin to 1 part of protamine zinc insulin) to be the best of the extemporaneously prepared mixtures. Colwell (1947) also favors the two-to-one mixture and so indeed apparently do most men. Colwell says that, contrary to popular belief, when the two insulins are mixed in these proportions a suspension of a new variety of protamine zinc insulin is formed, this compound representing an insulin-saturated protamine zinc complex that on injection releases its insulin more rapidly during the first twelve hours than during the second twelve hours; since the mixture is injected before breakfast its effect is therefore stronger than protamine zinc insulin during the day time and weaker at night. Colwell found it possible in a large series of severe diabetics to shift directly from protamine zinc insulin to the two-to-one mixture without a single indication for a preparation intermediate between theso two.

[illegible]

zinc insulin, and withdraw the empty syringe and needle; (b) inject air and [illegible]

be injected separately, but the control will not be nearly so good

New Experimental Mixtures.—MacBryde and Roberts (1943) are working with a specially modified protamine zinc insulin with 75 per cent slow and 25 per cent rapid effect, which is said to be accomplished by the admixture of equal parts of protamine zinc and regular insulin at *p*H 7.2. Colwell (1947) said that this preparation, now designated "NP50," has been shown in many clinical trials to be virtually indistinguishable from the two-to-one mixture, both showing unmistakably prompt reduction of sugar levels in four hours, attaining their peak effect in twelve to sixteen hours after injection, waning in effect appreciabl [illegible]
the second day [illegible]
(1947) also foun [illegible]
two. Unfortunately neither the two-to-one mixture nor the NP50 is sufficiently [illegible]

aration could be reached.

Globin Zinc Insulin.—Colwell (1947) said that the action of globin zinc insulin is demonstrable in two hours, that it reaches its peak in eight to twelve hours, and that the total duration of the effect is twenty-four hours at most. Since at its height the action is more intense than that of protamine zinc insulin but less intense than that of regular insulin, the globin zinc preparation may be considered to be intermediate in the promptness, intensity and duration of action between regular insulin and protamine zinc insulin. Colwell said that it is particularly useful in cases of mild diabetes in which the postprandial sugar level is high but the fasting level tends to be proportionately lower, it being more likely than protamine zinc insulin in his experience to provide good

control in such cases without nocturnal insulin shock. A serious fault many men find in globin insulin is the tendency of its effect to wane so rapidly in severe cases that an overnight rise in the sugar level occurs, heavy glycosuria appears before and after breakfast, and doses large enough to reduce the level promptly are prone to cause afternoon insulin shock. However, Roberts and Yater (1947) were usually able to control the hypoglycemic reactions by a small mid-afternoon feeding; in difficult cases in which very large doses of insulin were necessary, or in which the diabetic state was very labile, their best results were often obtained by giving two doses of globin insulin (about 70 per cent of the needed amount before breakfast and the rest at 3:00 P.M.

Globin zinc insulin is measured and injected like the other insulins but it should not be combined in the same syringe with protamine zinc insulin. Mixtures of globin zinc insulin and regular or crystalline zinc insulin seem illogical but they may have a place in the treatment of youngsters (see Diabetes in Children).

Systemic (Hypoglycemic) Reaction.—When an overdose of insulin has been taken the patient experiences a feeling of general muscular weakness, "hollowness" in the stomach accompanied by great hunger, subjective and objective trembling, paresthesias, restlessness and temporary loss of memory, sweating and pallor or flushing of the face, increased pulse rate, headache, nausea and vomiting. If regular or crystalline zinc insulin has been taken these symptoms may be experienced very suddenly or they may come on gradually during the course of a quarter-hour; if protamine zinc insulin has been injected the onset may be very much slower. In the more severe reactions the face assumes a masklike expression, there is diplopia and complete disorientation, and the patient may become unconscious and show a pronounced fall in temperature and blood pressure. Epileptiform convulsions are also seen in some instances; likewise a wide variety of behavioristic and mental changes foreign to the patient's normal personality may be manifested. Deaths have been reported but they are rare. However, there does exist a possibility of serious and permanent cerebral damage; Murphy and Purtell (1943) summarized twenty-six such cases from the literature and added one of their own. Other things being equal, the thin, frail, feeble patient is the most likely to develop reactions. Delayed absorption of food can certainly lead to hypoglycemic shock in a patient who has taken insulin before eating; since emotional disturbance is the chief cause of such delay, the advisability of maintaining as perfect emotional balance as possible for diabetics, especially at mealtimes, has been fully established.

The insulin reaction is commonly ascribed to a sudden hypoglycemia, but it is well not to overlook the fact that some other mechanism may also be involved since not all individuals in whom the blood sugar falls very considerably experience such a reaction, indeed, it has been said that reactions of this sort may occur with a normal or increased blood sugar. It has been suggested that not so much the hypoglycemia *per se* as the relatively greater dextrose impoverishment within the cell is to be held accountable, or that one might look upon an acute disturbance of the autonomic nervous system as the cause of the shock, of which hypoglycemia is only one of many symptoms. Unquestionably a very few of the reactions are allergic in nature, for they follow the use of one brand of insulin but not the use of another. It has been interestingly proposed in some quarters that severe repeated reactions are rooted to some extent in unstable cortical function. The electroencephalographic studies o

Greenblatt *et al* (1946) in some measure supported this positi...

from epileptic phenomena more often than do members of a normal group, and their electroencephalograms are essentially within normal limits, but Greenblatt *et al* found that 51 per cent of diabetic patients with frequent severe insulin reactions had abnormal encephalograms.

Dextrose.—Any carbohydrate out of which glucose (dextrose) may be quickly formed in the body is the antidote Orange juice is usually taken by the patient at home and it acts very well. One or 2 lumps of sugar, depending upon the size of the individual, quickly dissolved in the mouth are also effective in overcoming the symptoms. If the patient is unable to swallow easily, honey or corn syrup may be used. In any case, after a rest, the dose should be repeated.

Intravenous injection of dextrose may be made if the patient is unconscious, also it must sometimes be resorted to in patients who have not lost consciousness but in whom the hypoglycemia seems to be accompanied by a depression in the absorptive power of the intestinal mucous membrane (or should the failure to respond to the oral administration of dextrose be ascribed to acute peristaltic lapse?). Not more than 25 gm. should usually be given in this way in a solution of 5 to 50 per cent strength—500 cc. of 5 per cent, 250 cc. of 10 per cent, 125 cc. of 20 per cent, 50 cc. of 50 per cent; smaller amounts often suffice, but occasionally larger quantities need to be given. Joslin *et al.* (1940) said that in severe cases in which consciousness does not return within an hour it would probably be advisable to employ constant intravenous administration of 10 per cent dextrose solution to keep the blood sugar level at approximately 200 mg. per 100 cc.

The intracardiac injection of dextrose has been reported in one case by Imerman "The pulse was fast failing and the patient was moribund. Because of difficulty experienced previously in entering the veins of this patient, it ... further delay might be ... ort. This ... puncture ... ed to be at hand), and 10 cc. of sterile dextrose was injected. At the end of two minutes, the patient had recovered consciousness." As soon as possible, an additional 80 cc of the 20 per cent solution was introduced after a vein had been surgically exposed, immediate recovery was complete.

Protein—Protein, since 58 per cent of it is convertible into carbohydrate, ... of carbohydrate food, the ... content. ... ly feeble and by no means proportional to the theoretical value.

Epinephrine or Pituitrin.—Epinephrine (adrenalin) is effective in combating the insulin reaction, but in undernourished individuals carbohydrate should be given with it; indeed, there would seem to be little reason to use this drug when carbohydrate is at hand for in all cases its action is quite transient and must be reinforced by the subsequent taking of glucose. The epinephrine dose is 0.5 cc. in the child, and 1 cc in the adult, of the 1:1000 solution, given intramuscularly. Graham (1934) reported the effective use of pituitrin in 1-cc. injection.

Calcium.—Greiff (1931) reported two cases in which the giving of 1¼ ounces (40 gm.) of calcium gluconate daily, either by mouth or in enema, was effective in overcoming insulin hypersensitivity so that a daily injection of 10 units could be resumed, but I have seen no recent report of such employment of calcium.

Enforced Omission of Insulin or Food.—Under the wartime vicissitudes in bombed England consideration had to be given diabetics likely to be suddenly without either food or insulin. The advice of Lawrence (1940) may be briefly

able as a general rule for the severe diabetic to take one-third to one-half his usual insulin without food, taking the usual meal and insulin as soon as food becomes available or the usual food and only a half dose of insulin if the preceding dose had been taken within six hours

Insulin and Exercise.—Exercise exerts a very profound effect upon the diabetic Even before the inauguration of the insulin era it was known that the mild diabetic was improved and the severe diabetic made worse by exercise.

was shown, however, by Soskin *et al* (1934), whose two carefully studied patients did not show significant decreases in insulin requirements during a systematic course in physical training. Furthermore, Marble and Smith (1936)

insulin and breakfast

during the succeeding ten days apparently as a result of marked reduction in the salt of the diet; insulin dosage had remained practically the same. It is said that the edema can sometimes be made to disappear by dropping down

with the insulin dosage and gradually building up again. If alkaline therapy is being employed it should be stopped.

Insulin Resistance.—Considering the enormous number of individuals the world over [illegible]

spond to th [illegible]

spond, is ce [illegible]

have been recorded. A few typical cases may be instanced: Taussig's case was given as much as 1100 units in one day without becoming *sugar-free; after* several months, however, the response to insulin showed considerable improvement. Lawrence's nineteen-year old patient required 400 units per day to reduce his blood sugar to normal and to keep him sugar-free; the patient of Mohler and Goldburgh suddenly lost his responsiveness and died of diabetes after forty days of 437 units daily insulin dosage, upon the other hand, the patient of Karr *et al.* in whom over 600 units daily did not keep the blood sugar under 200 mg., suddenly lost her resistance following the injection of a foreign protein (the serum of a rabbit that had been sensitized to a mixture of the [illegible]

patient was resistant to protamine zinc insulin but not to regular insulin; Wiener's patient required as much as 3250 units in twenty-four hours, but [illegible]

month period during which he was given from 500 to 2460 units of insulin daily, there was some evidence of the presence of an insulin antagonist; Felder found an insulin inhibiting factor in the serum of his patient at the height of the insulin resistance, but McGavack *et al.* failed to do so in their case. Hendry has recorded a case in which great reduction in response to insulin was corrected by the use of thyroid substance, the patient having manifested a slight hypothyroidism; but the opposite picture is more usually seen, *i.e.*, insulin resistance associated with hyperthyroidism. The possible role of suprarenal and hepatic disorders has been discussed by several authors and also the direct association of hypophyseal (pituitary) disturbance with insulin resistance. Pullen and Sodeman felt they accomplished something by irradiation of the pituitary gland in their case that was associated with probable pituitary basophilism Spiegelman treated nine diabetic women with estrogenic hormone as used in the handling of the menopause and effected a diminution in their insulin requirement, a type of therapy that conceivably could be helpful in some cases of insulin resistance. Some of the cases are in association with hemochromatosis, others with specific infections such as tuberculosis and syphilis, or with rheumatoid arthritis. All explanations of insulin refractoriness upon a single basis are still highly speculative. It seems that the highest recorded quantity of insulin ever administered was the 5000 units given in [illegible] years of treatment [illegible] age daily dose of [illegible] allergizing factor, usually infectious, provoked a fluctuating anti-hormonal effect against the insulin.

Insulin Allergy.—Instances of insulin allergy are observed with much greater

one. Goldner and Ricketts (1942) thought that since interrupted insulin treatment seems to predispose to allergy, the performance of skin tests might be advisable in all patients who resume insulin treatment

TABLE 14.—RAPID DESENSITIZATION WITH LILLY'S REGULAR INSULIN (BAYER)

Units	Time.	Reaction
1/100	9 15 A M	++
1/100	9 45	++
Sterile distilled water	9 47	0
1/200	10 16	+
1/200	10 46	++
1/400	11 20	++
1/1000	11 42	+
1/1000	12 20 P M	±
1/500	1 30	+
1/250	2 03	±
1/125	2 32	±
1/66	3 04	±
1/50	3 36	0
1/25	4 02	0
1/10	4 16	±
1/5	4 30	±
1/2	4 45	±
1	5 01	0
5 (hypodermically)	5 20	0

++ denotes wheal of at least 1 cm with surrounding hyperemia, +, wheal of less than 8 mm with surrounding hyperemia, ±, no wheal, faint hyperemia, 0, no reaction

Some of the cases are arrested at once, insofar as the allergic response to insulin is concerned, by changing from protamine insulin to globin insulin, or by changing brands of the drug, *i.e.*, changing from a brand prepared from beef pancreas to one prepared from pork pancreas, or *vice versa;* changing to crystalline insulin may also be all that is required. Gastineau and Leavitt (1946) reported a case at the Mayo Clinic in which benadryl administered orally afforded almost complete relief of local and generalized urticaria while a dilute solution of benadryl mixed with insulin prevented local reaction; equal amounts of insulin and a 1:1000 solution of benadryl were used for the local injections.

dose every other day; after three months both of their patients were able to tolerate 15 units twice daily, but desensitization lasted only one month. (c) Bayer (1934), using Lilly's regular insulin, known to contain both beef and pork, made up to suitable dilutions with sterile distilled water, successfully desensitized an individual in eight hours, at least insofar that the patient was thereafter able to use insulin though slight local and general reactions recurred

TABLE 15.—METHOD OF DESENSITIZATION (WEITZ)

Date.	Time	Insulin units.	Reaction.	Urine.		Blood.	Adrenalin (minims)
				Sugar	Acetone		
10/ 3/40	11:00 A.M.	0.1	Wheal 2 sq. cm.	4+	0	306	
	11.20 A.M.	0.1	Wheal 4 sq. cm.				
	11:50 A.M.	0.2	Wheal 4 sq. cm.				
	12:20 P.M.	0.4	Wheal 6 sq. cm.				
	12:50 P.M.	0.6	Wheal 6 sq. cm. with induration				
	1:20 P.M.	0.8	Induration, slight				
	1:50 P.M.	1.2	Induration, slight				
	2:20 P.M.	1.6	Induration, moderate				
	2.50 P.M.	2.0	Induration, marked				
	6:00 P.M.	2.4	Induration, marked	+	0		
	6:30 P.M.	2.8	Induration, marked				
	7:00 P.M.	3.2	Induration, marked				
	7:30 P.M.	3.6	Urticaria, slight				
	8:00 P.M.	4.0	Urticaria, marked	4+	0		5 × 2
10/ 4/40	8:30 A.M.	4.0		4+	0	267	
	12:45 P.M.	4.0					
	5:15 P.M.	*4.0*	*Urticaria*	4+	*0*		*5*
10/ 5/40	8:00 A.M.	6.0		4+	0	254	
	12:00 noon	6.0	Urticaria, slight	4+	0		3
10/ 6/40	8:00 A.M.	4.0		4+	0		
	12:00 noon	4.0	Urticaria, slight	4+	0		3
10/ 7/40	8:00 A.M.	4.0		4+			
	5:00 P.M.	4.0	Urticaria, slight	4+			
10/ 8/40	8:00 A.M.	6.0	Negative	4+		240	
	5:00 P.M.	6.0	Negative	4+			
10/ 9/40	8:00 A.M.	8.0	Negative	3+			
	5:00 P.M.	8.0	Negative	3+			
10/10/40	8:00 A.M.	10.0	Negative	2+		188	
	5:00 P.M.	10.0	Negative	2+			
10/11/40	8:00 A.M.	10.0	Negative	Trace			
	5:00 P.M.	10.0	Negative	1+			
10/12/40	8:00 A.M.	10.0	Negative	0		124	
	5:00 P.M.	10.0	Negative	0			

at intervals (see Table 14); Corcoran (1938), and Ulrich *et al.* (1939), reported cases rapidly desensitized in somewhat the same manner; Weitz *(1943) desensitized* his case in a matter of a few days by the method indicated in Table 15 (d) Collens *et al.* used histamine phosphate in one case, beginning with a subcutaneous injection of 0.1 mg. and repeating the injection thrice weekly with such increasing dosage that the patient received 1 mg. on the eighth injection,

section on the Allergic Disturbances) in one case and mentioned eleven other cases in which they obtained "varying results"

A few cases of insulin allergy, be it noted, have become spontaneously desensitized. Also, there are reports of diabetes ameliorating when the patient has become allergically sensitive to insulin

Local Reactions.—A few cases of extensive atrophy of subcutaneous fat following repeated insulin injections have been reported. Less extensive involvement, especially in women and children, is by no means rare—Joslin *et al.* (1940) said that this local reaction occurs in nearly 30 per cent of their diabetic children; spontaneous recovery seems usually to occur in two years but no proved method of prevention or correction has been reported. Much rarer is the development of small lipomatous growths at the site of injection What it is that predisposes certain individuals to this reaction is also unknown

Local reactions of an annoying nature sometimes occur with protamine zinc insulin, but the incidence of these reactions is lessened almost to the vanishing point if alcohol is not used to sterilize the injection outfit and especially if the injections are given deeply beneath the skin; it is best to pinch up the skin and then inject at right angles into the triangle thus formed. The injection of globin zinc insulin occasionally causes a burning sensation

ACIDOSIS AND COMA

When the ketone bodies begin to build up in the blood the kidneys secrete acids in the free form and also as ammonium salts; furthermore some of the bicarbonates of the blood are split up to yield base for neutralizing purposes, the liberated carbon dioxide being eliminated by the lungs When these mechanisms alone fail to keep pace with the production of acids, the fixed bases begin to be called upon and the body loses sodium—since this latter step really amounts to a decrease in total salt concentration there results a state of dehydration because water is excreted to maintain isotonicity in the tissues. Hence the patient is acidotic (due to reduction of the alkali reserve of the blood), hyperpneic (the liberated carbon dioxide must be eliminated) and dehydrated (because of the sodium chloride loss). The very obvious aims of

because it (a) promotes the oxydation of glycogen, (b) supplements the action of insulin, (c) reduces the destruction of protein and (d) diminishes the production of ketone bodies; and Danowski *et al.* (1946), of the Yale group, have pointed out that the contention of the Joslin group that glucose *per se* is harmful in early diabetic acidosis is based upon cases that really demonstrate the results of inadequate salt therapy rather than the toxic effects of glucose. I shall therefore continue in this edition of the book to describe a means of combating diabetic acidosis and coma that incorporates the administration of glucose as an integral part of the plan.

But now what plan? Well, it seems to me that Almy, Swift and Tolstoi (1945), of the New York Hospital and Cornell Medical College, made a fine practical contribution when they described their method of treating diabetic [illegible]

index of the severity of the disorder or of the progress of the treatment for the reason that such determinations are of no value when glucose is administered as a part of the treatment. And they do not routinely use the carbon dioxide-combining power of the blood in gauging the severity of the state because, while not denying that a well-run determination by an experienced technician is an accurate index of the severity of acidosis at the time it is taken and may outweigh in accuracy the impression gained from observing the respirations and the state of consciousness of the patient, they nevertheless find that since *the result of such determinations are often not available until from* one to three hours after the sample is taken they are in many instances only of academic interest In most clinics it is the rule to administer large doses of insulin at a time, but there is no general agreement as to precisely how large this dose should be, and indeed in any case the dosage must be empirically derived since the maximal rate of utilization of insulin is not known. In the plan of Almy *et al.* small doses of insulin are given and repeated frequently, it being thought that there is thus accomplished a more efficient use of the insulin since it is well known that the law of diminishing returns applies to [illegible] per unit than

[illegible]

effect of large doses of insulin.

The results achieved by Almy *et al.*—a mortality rate directly ascribable to diabetic acidosis of only 1 per cent in their ninety-nine instances of acidosis [illegible] can be shown in any [illegible] by [illegible] lied [illegible] nds [illegible] hat [illegible] nts

were *unconscious or semi-conscious, yet the fact seems* to be that the unconscious patients were handled with as great ease as those who were conscious [illegible] licating condi-

[illegible]

Insulin, Glucose, Salt and Fluid.—1. As soon as the diagnosis is made, give 25 units of regular insulin subcutaneously and repeat this injection every half hour until the patient is free from all signs of ketosis as judged by clinical and laboratory evidence.

2. When it is possible to do so, replace fluid, salt and carbohydrate by mouth, giving in each hour (a) 50 to 75 gm. of glucose as orange juice (500–700 cc.), grape juice (300–450 cc.), or fortified fruit juices; (b) salty broth, 200 cc.; (c) *enough water to make the total fluid intake 1000–1500 cc.*

3. If the patient is drowsy or comatose, or has vomited or been nauseated during the preceding twenty-four hours, begin the therapy by the intravenous [illegible]

extreme care for signs of increased venous pressure and passive congestion of the lungs. *Return to the oral route of administration as soon as the patient* is fully conscious and free from nausea.

4. Test a urine specimen every half hour or every hour for sugar, acetone and diacetic acid, catheterizing the patient if necessary. Continue the foregoing therapy until the urine is free from acetone and diacetic acid (and do not leave the ward until this is accomplished)

5. When ketonuria and all clinical signs of acidosis have disappeared give fruit juice and 25 units of insulin at two-hour intervals for at least eight more hours.

6. *If the patient is anuric, or in the exceedingly rare instances in which* there may be acidosis without the presence of acetone bodies in the urine, guide the therapy by frequent estimations of the carbon dioxide-combining power of the blood

The Use of Alkalis.—It seems to me now to be the opinion of practically all [illegible]

sodium lactate solution should be used in twenty-four hours, and that thereafter the injections are to be just of physiologic saline solution. If a sodium lactate solution is not available one may boil 500 cc. of freshly distilled water, remove from the flame, add 25 gm of sodium bicarbonate from a previously unopened package, dilute the solution with an equal volume of sterilized physiologic saline solution, and allow to flow into the vein during one hour.

Lavage, Cleansing Enema and Warmth.—In most hospitals, lavage of the stomach is employed routinely nowadays as soon as beginning coma is diagnosed; time has shown the procedure to be of great value, for a dilated or partially filled stomach is a great handicap to one who during the succeeding twenty-four hours must grapple catch-as-catch-can with death. Root and Brigham (1947) said the fact that a patient has not vomited is not a contraindication to lavage because all too often the death of a patient in coma has

been attributed to pulmonary edema when in reality the *râles at the bases of* the lungs were due to gastric contents that had been aspirated or had flowed into the lungs; in their experience a large Ewald tube is to be preferred to the small duodenal tube. Ordinarily a saline cleansing enema should be given as soon as possible. Of course the patient should be kept warm by all the devices usually employed in treating a case of shock—nearly all of these patients have a subnormal temperature at the beginning of coma, and an individual with subnormal temperature is not well armed for a fight.

Circulatory Stimulation and Transfusion.—A patient not improved by judicious application of the methods discussed above is not likely to be helped by the employment of such stimulants as epinephrine, ephedrine, metrazol, coramine, caffeine, benzedrine, and so on, though it is admittedly difficult not to employ these drugs. The transfusion of whole blood or plasma must sometimes be resorted to when there is definite evidence of peripheral circulatory failure.

Combating Potassium and Magnesium Deficiency.—Holler (1946) reported an extreme instance of diabetic coma during which the value for serum potassium was reduced to a very low figure and the patient developed weakness of the extremities and of the muscles of respiration. Prompt improvement and eventual recovery occurred after the intravenous administration of potassium chloride, first in the form of 1.5 gm. in 2 per cent solution in distilled water intravenously over a period of thirty-five minutes, and later in the form of a subcutaneous infusion of 200 cc. of the 2 per cent solution mixed with an equal amount of physiologic saline solution and accompanied by the administration of 2 gm. of potassium citrate by mouth followed by 1 gm. at hourly intervals for two subsequent doses. Martin and Wertman (1947) have since found a considerable fall in serum potassium levels during therapy in nearly half of fourteen patients in severe diabetic acidosis; in about a third of the patients there was also a fall in serum magnesium concentrations. They felt that their findings indicated that patients in whom the potassium and magnesium levels are low should receive adjunctive potassium and magnesium therapy, but they also warned that this might be a dangerous procedure if the patient is in shock with decreased renal function.

TREATMENT OF COMPLICATIONS

Intercurrent Infection.—It is well known that an acute intercurrent infec-

intervals. They stop the use of protamine zinc insulin but give the same total dosage of insulin in the form of crystalline insulin only, dividing the total dosage for the day into equal parts given before each of the feedings and increasing the dosage as seems indicated. When the peak is reached and the diabetes controlled, reductions in the insulin are then imperative to prevent the hypoglycemic reaction, and then with recovery the former diet and insulin are

...protamine zinc insulin in the presence

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Chemotherapeutic Agents, such as the arsenicals, the sulfonamides and penicillin, may be employed in the diabetic just as in the nondiabetic. Baldwin and Root (1940), discussing urinary tract infections, also spoke of the free use of ammonium mandelate and methenamine (urotropin) and also ammonium chloride as an acidifying agent.

Tuberculosis is no longer looked upon as making prognosis hopeless; McKean *et al.* (1941) felt that mortality in cases of associated diabetes and tuberculosis parallels closely that of tuberculosis alone, an opinion supported by the rather coy statement of Foley and Andosca (1944) that they invariably give a poor prognosis in the case of a diabetic with far advanced tuberculosis even if the diabetes is controlled Banyai and Cadden (1944) authoritatively stated that the indications and contraindications for pulmonary collapse therapy are the same for diabetic as for nondiabetic tuberculous patients but that, because of the frequency with which empyema complicates artificial pneumothorax in persons with predominantly exudative recent tuberculous lesions, the use of this measure is greatly limited for tuberculous diabetic patients

vidual.

Gastro-intestinal Disturbances.—Acute gastro-intestinal upsets are dan-

dosage and as careful watch as possible be kept on the levels of sugar in the blood and urine. Diarrhea is also a serious matter because it also robs the patient of food and fluids. Here again the result may be ketosis or it may be hypoglycemia, the former if the deprivation of carbohydrate causes the breakdown of body tissues, just as in the case of vomiting and inability to eat, the latter because the low state of metabolic activity of the body may render

in sprue.

Cardiovascular Complications.—The majority of the foremost students of diabetes agree that in advanced arteriosclerotic, hypertensive, peripheral, vascular, or coronary disturbances insulin should be employed with great caution, since sudden lowering of the blood-sugar level seems to be particularly difficult for such diabetics to combat. True anginal pain subsequent to insulin

stimulation, though the mechanism of the effect is not clear. An extension of

these studies is certainly to be desired before one can unreservedly recommend combined prostigmine-insulin therapy in diabetics with diminished cardiac reserve. The observation of Weinroth and Herzstein (1946), that in a group of 301 male diabetic patients the incidence of thrombosed peripheral arteries was significantly higher in smokers than in non-smokers, seems to me important.

Neurologic Complications.—Neurologic complications are not infrequent in diabetes and they may be of all kinds from the mildest to the most severe. There seems to be an unusual tendency of diabetic neuropathy to involve the autonomic nervous system, with such resultant diverse clinical manifestations of neuritic disease as Charcot joints, gross disturbances of the gastro-intestinal and genito-urinary functions, abnormal blood pressure regulation, bone changes of an atrophic nature, etc. Many patients with peripheral diabetic neuropathy develop serious foot infections. Rundles (1945) said that in twenty-five of the 125 cases of diabetic neuropathy studied by him among some 3000 diabetic patients at the University Hospital in Ann Arbor, Michigan, there had been no diabetic treatment at all before the hospital admission, and that of the remaining patients who had some treatment everyone seemed to have received what would have been called poor treatment. Or one may say this in other terms, *i.e.*, the prevention in so far

of the di

the treat

need for insulin accompanied the development of the neuropathy, and this increased need often persisted permanently. He said he had seen no benefit from the addition of vitamin supplements unless there were clinical indications apart from the neuritic disease for such medication. However, Rudy and Epstein (1945) gained the impression from the study of 100 cases followed for one to ten years that the symptoms and signs of vitamin B-complex deficiency are frequently present and that prolonged therapy with vitamin B-complex is valuable supplementation of the diabetic control itself. The report of Biskind and Schreier (1945) that intensive and persistent vitamin B-complex therapy frequently makes possible a reduction in the insulin requirement of diabetic patients lacks confirmation.

Treusch (1945) has classified the diabetic neuropathies into four groups. In group one, "diabetes with pain," are patients whose complaints are aching

ic neuropathy," there is vascular sclerosis with arterial insufficiency of some degree, and pain, paresthesia and cramps, occurring especially at night, constitute the main symptoms, with the legs being primarily involved with progressive increase in involvement peripherally. In this group Treusch said there will occasionally be considerable improvement after many months if the vascular status of the extremity can be improved. In group three,

definite objective signs are demonstrable, and the process is frequently diffuse. In this group with usual diabetic control and whatever supportive measures seem indicated definite improvement is said usually to occur in

weeks to months In group four, "diabetic visceral neuritis," are the cases in which there is involvement of the autonomic nervous system, the symptoms consisting of burning paresthesia of the feet in the absence of objective neurologic signs and in the presence of such objective vasomotor changes as would occur after sympathectomy.

In some instances it appears that diabetic neuritis unfortunately and paradoxically makes its appearance at the time when the patient's diabetes is first brought under control with insulin

Eye Complications.—The principal ocular complications are: (1) transient changes in refraction, which are unimportant and apparently occur as frequently with as without insulin, (2) diabetic cataract, which seems to have decreased in incidence since insulin came into use, (3) lipemia retinalis, which is now rarely seen, (4) toxic amblyopia, which has also much decreased under careful insulin management, and (5) diabetic retinitis This latter involvement has apparently become more prominent under the new type of treatment, possibly largely because more diabetics are living into the arteriosclerotic age So far it has not been conclusively demonstrated whether high carbohydrate-low fat and liberal insulin therapy has served to control the progress of this serious complication An excellent symposium on the subject appeared in the American Journal of Digestive Diseases in September, 1943.

Pruritus and Furunculosis.—These two dermatoses are frequent complications in diabetes, the former always very annoying, the latter often very serious. Their treatment is described in the chapter on skin diseases

SURGERY IN DIABETES

McKittrick (1946), of the group at the New England Deaconess Hospital, said that increasing experience had convinced him that diabetes mellitus does not contraindicate any surgical procedure whose indications are clear, provided always that the medical, surgical and hospital teamwork is such as to insure efficient, cooperative care of the patient's metabolic disturbance. He said that penicillin has been most helpful in the treatment of carbuncle, often resolving large lesions into small painless fluctuant areas 2 or 3 cm. in diameter that have healed promptly after local excision, lesions of the type that at the worst would have resulted fatally in 5 to 10 per cent of cases prior to the use of penicillin and at best would have cost the patient weeks of hospital care as well as a wound requiring months for final healing The advent of the sulfonamides and more recently of penicillin has also much improved the mortality figures in patients having leg lesions requiring major amputations or foot lesions requiring minor amputations McKittrick uses spinal anesthesia for all his operations on the lower extremities in diabetics.

Preoperative Care.—If the patient is under good diabetic control and is coming up for an elective operation, the only preliminary alteration in surgical orders usually necessary is to have him given 6 to 10 ounces of orange juice and 10 to 20 units of insulin two hours before operation, adding 10 gm. of dextrose intravenously with another 5 units of insulin just before or during the operation if the carbon dioxide-combining power of the plasma is less than 0 volumes per cent If the patient is not under diabetic control, or if the operation is of an emergency nature or complicated by infection, the treatment had better be that of acidosis with threatened coma The diabetic coming operation for the relief of a complicating hyperthyroidism had best be treated as though his diabetes is complicated by infection, for hyperthyroidism

like infection decreases the power of insulin; with the relief of the hyperthyroid state the severity of the diabetes is nearly always much ameliorated.

Postoperative Care.—The total amount of insulin which the patient has been taking preoperatively in twenty-four hours should be given in the twenty-four hours succeeding operation, with this difference only that it is best to divide it into smaller portions and inject every three or four hours; during the twenty-four hours the patient should receive in the form of intravenously administered dextrose the amount of carbohydrate customarily allowed in his diet. Thereafter, dietary readjustment must be made, bearing in mind that the patient not infrequently after operation requires for a while somewhat different insulin dosage than before. The appearance of sugar in the urine at any time shortly after operation, or the signs of hypoglycemia or acidosis, of course require complete accommodation of the treatment to the new conditions.

DIABETES IN CHILDREN

The advent of insulin made it possible to treat childhood diabetes with as good success as adult diabetes; the new high carbohydrate-low fat diets have simplified the problem and much eased the parental burden. Joslin (1947) said that his group had 237 out of an original 249 with the onset of diabetes in childhood who had survived twenty years, this being ten times as long as the survival period of their fatal childhood cases between 1914 and 1922. However, practically all childhood cases are relatively severe. Insulin requirements are also higher than for an adult with diabetes of comparable grade, but there is no definite proportional gauge and therefore dosage must be evolved according to the needs of the individual patient. The approach of puberty, especially in girls, often accentuates this difference between childhood and adult utilization of the drug; after sexual maturity has become established, reduction in dosage is usually possible.

Choice of Insulin.—Mosenthal and Rosen (1947), reporting a study of 126 children in a summer diabetic camp, said it was found that of the three types of insulin, regular, protamine and globin, only protamine and globin were satisfactory when given alone; in many instances regular insulin was a distinct failure. They found the two-to-one regular-protamine mixture, prepared extemporaneously in one syringe, the most satisfactory type of injection. However, they thought that more extensive study might have shown globin insulin alone to yield equally good results since the diet regimen with snacks between breakfast and lunch, between lunch and dinner, and at bedtime, besides the three regular meals, would probably be a system of feeding particularly adapted to the use of globin insulin—and for that matter to the requirements of the two-part regular one-part protamine mixture, which has an effect a good deal like globin in their opinion. Boyd (1947), at the University of Iowa, said that he and his group have concluded that protamine zinc insulin is poorly adapted to the needs of the diabetic child since it has not been possible with it to avoid undesirable fluctuations of blood sugar levels through the use of a single daily injection. He is currently employing globin insulin together with regular insulin and thereby frequently avoiding the need for a night dose; two or three daily injections are given, using regular insulin as the basis for therapy and globin insulin as a supplementary agent.

Exercise.—Proper management comprises full utilization of the insulin-sparing function of exercise, but with the greater lability of childhood meta-

bolic processes the omission of exercise at accustomed times is more dangerous than in adults. Setting-up exercises of definite type and duration have been shown to be well worth instituting during those seasons when spontaneous outdoor exercise is restricted or for routine performance throughout the year by children not temperamentally disposed to be very active It is well to bear in mind that if the child's treatment is standardized during a preliminary period in hospital, he will require to have his insulin dosage reduced when he returns to normal play activity at home.

Infection.—The effect of infection in reducing insulin efficiency is much more rapid and more marked in children than in adults since children have a relatively smaller reserve of glycogen in the liver A child completely free of glycosuria, hyperglycemia and acidosis one day may be in coma the next as a result of even the milder sort of acute infectious process. Mirsky and Nelson (1944) stressed the importance of frequent feedings of carbohydrate during infections in children.

Acidosis, Coma and Hypoglycemia.—As just stated, the transition from a state of complete control to one of coma may be extremely rapid in children in whom a rigid diet-to-insulin regimen is being followed, a food orgy, or the omission of a dose of insulin, can institute it as rapidly as the onset of infection

commission Some physicians, feeling that the symptoms of impending shock form a pattern typical for each individual, like deliberately to induce such an experience for educative purposes during the early period of diabetic training, however, that the identical prodromata always appear is denied by many observers

DIABETES AND PREGNANCY

Effect of Diabetes upon the Mother.—Insulin has unquestionably increased the fertility of diabetic women and it is now the consensus that the fact of pregnancy itself does not offer a very great threat to the life of the diabetic woman provided she is in the hands of a physician who thoroughly understands the treatment of diabetes and is herself fully cooperative, among the 322 consecutive pregnancies in diabetic women observed by White (1947) in Joslin's clinic between January 1936 and November 1946, there was one

twenty-five years' duration This opinion of White is based upon the observation of women who have had diabetes for that length of time, the disease having begun in their childhood, indicating that the incidence of vascular disease is high as is also the incidence of the toxemias of pregnancy; the course of pregnancy in these women after twenty-five years of diabetes was more complicated than in earlier pregnancies and the fetal survival rate low. In the pregnant diabetic the changes in tolerance, necessitating dietary and insulin adjustments, are not usually predictable, though in the studies of

level at, or shortly before, term. Women do not always react similarly in each pregnancy: Northmann (1941) reported a patient whose first pregnancy terminated in coma whereas during the course of the second pregnancy there was a remarkable improvement in carbohydrate utilization; Feinblatt *et al.* (1944) also reported five cases in which the women became dramatically insulin-sensitive during the immediate postpartum period.

Nausea and vomiting during the first trimester demand readjustments to prevent ketosis. Many men handle this situation by hourly feedings and the administration of insulin every three hours if the patient is on regular (or crystalline) insulin, giving supplementary dextrose intravenously if necessary. Patients on the two-to-one regular-protamine mixture are usually given extra doses of regular (or crystalline) insulin before lunch and the evening meal in the attempt to prevent the excretion of glucose that is often excessive due to the lowered renal threshold in pregnancy; it seemed from the report of White and Hunt (1943) that this latter procedure was practically routine in Joslin's clinic.

Prolonged difficult labor, which occurs more frequently among diabetic than non-diabetic women because of the overweight of the child, centers attention upon the actual period of labor as the most trying from the diabetic standpoint. Not only is there the possibility of a plunge into hypoglycemic shock upon the one hand or ketosis and coma upon the other, but the possibilities of perineal or cervical tears and of portpartum sepsis are undoubtedly greater causes for concern in the diabetic than in the non-diabetic woman Many observers have felt that cesarean section at about the thirty-sixth to thirty-seventh week is indicated in most instances, but the opinion is not unanimously held.

Diabetic women are seldom able to nurse their infants, when lactation begins one should be on guard against a blood-sugar drop, necessitating reduction in insulin dosage

Effect of Diabetes Upon the Infant.—If we make an exception of White's (1945) report of a fetal or a newborn infant death rate of only 16 per cent, a

[illegible]

betic group Even under the most favorable conditions the risk to the infant was about four times that of the normal, and if the mother had severe complications of pregnancy with diabetes, either mild or severe, the risk was about eight times as great. These figures seemed to hold whether the mothers were or were not insulin treated. The excessive size of the fetus in diabetic women has been held responsible for part of the high mortality in infants by some

[illegible]

since fetal and newborn deaths occurred with about the same incidence before diabetes became manifest in the mother as afterward. Miller and Wilson (1943)

found that infants born of diabetic mothers may have cardiac hypertrophy and excessive erythropoiesis in the liver with large numbers of nucleated red blood cells in the peripheral blood during the first days of life, the cardiac and

mothers, they felt furthermore that there is no certainty that the lethal factor

Hospital in New York they found that the first five-year pre-diabetic period revealed an increased fetal and neonatal mortality but the preceding fifteen years was not characterized by such a tendency and that the total rate for the entire twenty-year pre-diabetic period did not differ significantly from normal Dolger (1945) felt that this viewpoint agreed with White's data indicating that women are normal in their childbearing capacity until they develop diabetes White (1945), however, said that she was unable to make the comparison on this basis because her own series of patients was largely derived

the present be left to be reconciled between these two groups of observers.

White and Hunt expressed themselves of the opinion, in 1940, that fetal deaths in diabetic women are associated with a high concentration of gonadotropic substance in the maternal serum during the latter part of pregnancy and that the administration of estrogens and progesterone can prevent the large number of fatalities. In 1947, White reported that among seventy pregnancies classified as normal by the level of serum chorionic gonadotropin and by the urinary excretion of pregnandiol the fetal survival was 97 per cent and the incidence of preeclampsia was 1 per cent, in sixty-two cases in which the sex hormonal pattern was abnormal and uncorrected the fetal survival was 44 per cent and the incidence of preeclampsia was 50 per cent In 190 cases the abnormal balance of the sex hormones was corrected by substitutional estrogen and progesterone therapy, the incidence of preeclampsia falling to 5 per cent and the fetal survival rising to 90 per cent

THE TOLSTOI PLAN OF DIABETIC THERAPY

This relatively new plan of diabetic therapy involves a very wide departure from previously accepted practice in that it does not look upon absence of

Lavietes *et al.* (1943) of thirty-one pregnancies in twenty-three diabetic women carbohydrate tolerance was observed to fall quite regularly, the most marked fall usually beginning at six to eight months with return to the original level at, or shortly before, term. Women do not always react similarly in each pregnancy: Northmann (1941) reported a patient whose first pregnancy terminated in coma whereas during the course of the second pregnancy there was a remarkable improvement in carbohydrate utilization; Feinblatt *et al* (1944) also reported five cases in which the women became dramatically insulin-sensitive during the immediate postpartum period.

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pregnant

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regarding slight to moderate hyperglycemia and glycosuria. Here in our own country Bruce is using the "free" diet with great satisfaction in children. His children are put on a carefully weighed diet at first, but after a month or two are told to measure their food in teaspoons and tablespoons and ounces, being kept of course under close observation and checked at monthly intervals After a year of carefully measured diet, the patient is then put on a "free" diet. By this is not meant that he is allowed to eat any and everything he

parents should know calories and food values and diabetes so well that they can handle the situation with great ease He has the urine examined twice a day, the specimen on arising should contain no sugar; the one at bedtime should contain a good deal of sugar, but no acetone. It is said that the children on these "free" diets are doing beautifully. They are in splendid health, go to parties and take part in athletics, and do what their playmates do. Indeed, except for their daily dose of depot insulin (Bruce kindly informed me, in early

any ill effects from this method of treatment.

firmly established that the lax control of the disease is responsible for the degenerative complications that characterize it, there is nevertheless in existence suggestive evidence in both animals and man that this may be the case, he therefore felt strongly that in the absence of proof to the contrary it is unsound and hazardous to abandon the goal of normal glycemia in the treatment of diabetic patients. Lukens' (1947) viewpoint was much the same, namely that while no single patient can be promised exemption from the severe complications of diabetes no matter how well he is treated, nevertheless after a quarter of a century of experience with insulin evidence is beginning to appear that the degree of control has an effect on some of the late complications, he therefore felt that in any case a deviation from the high standard of regulation should be made only with reluctance. Of course it is to be expected that Joslin (1947) would be in complete opposition to this new type of therapy and would remark that those who advocate free diets for children, disregarding hyperglycemia and glycosuria so long as acetonuria is absent, as yet have not published the status of their children after twenty years. Nevertheless, I am much interested in this Tolstoi plan of therapeutic approach and so are many physicians throughout the world, and by and by the twenty years will have passed

upon this premise is Tolstoi, who, at the time of his first comprehensive report in 1940, had treated eighty-four patients without an attempt to "desugarize" In 1946, Tolstoi reported that the treatment had been in routine employment at *his clinic at the New York Hospital* for about a decade. When a patient presents symptoms as well as glycosuria, he is put upon a diet that seems to conform just about to the ordinary family diet except that it excludes candies, cakes, pies and ice cream and aims as a general average at protein 90 gm., fat 85 gm., carbohydrate 250 gm., and he is started off with 15 to 20 units of protamine zinc insulin. If the patient remains symptom-free, maintains his weight, or gains in weight in instances in which that seems desirable, and has no acetone in the urine on the diet and this amount of insulin, and if furthermore he is socially and economically useful, his treatment is considered satisfactory regardless of the amount of glycosuria he may have. If, however, in addition to his glycosuria he is losing weight on an adequate diet, or in addition to the glycosuria has such symptoms as thirst, frequency, or weakness, the

a slight trace of acetone will appear in the urine. This patient is not hospitalized, particularly if he has been trained, but instead he is told to take salty broths freely, and is given 7½ grain (0 5 gm.) tablets of sodium chloride, 2 tablets to be taken every two or three hours, following each with a glass of water. He is told to test his urine at each voiding and as long as acetone continues to be positive to supplement the basic daily dose of protamine with regular insulin. If the test for sugar is 4+, he is to inject 25 units of insulin; if 2 to 3+, 15 units, and if negative, he is to take the juice of an orange This

peutic standpoint and glycosuria is disregarded He does emphasize, however, the importance of maintaining weight, freedom from symptoms and absence of ketosis, and he also warns the patient of the seriousness of any infection or gastric upset and of the importance of never reducing or discontinuing the use of insulin unless so ordered.

Tolstoi has had patients on this type of treatment for about a decade and has not found any clinical support in his experience for the traditional dicta

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minor and major surgical procedures just as well as those treated according to

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Hopkins, that neither the value for blood sugar nor the degree of glycosuria is an adequate criterion for the regulation of diabetes. In Ireland, Micks (1943) reported that for the past eight years none of his diabetic patients had been on a

to eat what it wanted and givin

regarding slight to moderate hyperglycemia and glycosuria. Here in our own country Bruce is using the "free" diet with great satisfaction in children. His children are put on a carefully weighed diet at first, but after a month or two are told to measure their food in teaspoons and tablespoons and ounces, being kept of course under close observation and checked at monthly intervals After a year of carefully measured diet, the patient is then put on a "free" diet. By this is not meant that he is allowed to eat any and everything he wants without exercising any judgment or self-control; he must try to follow the diet he used when it was measured, but without being a slave to it. Bruce makes the point that after a year of training an intelligent child and his parents should know calories and food values and diabetes so well that they can handle the situation with great ease. He has the urine examined twice a day, the specimen on arising should contain no sugar; the one at bedtime should contain a good deal of sugar, but no acetone It is said that the children on these "free" diets are doing beautifully. They are in splendid health, go to parties and take part in athletics, and do what their playmates do. Indeed, except for their daily dose of depot insulin (Bruce kindly informed me, in early 1947, that he was then using globin instead of protamine insulin), they lead a normal life. And their parents are unanimous in their feeling that their children are happier and are now like normal children since going on the "free" diet. Bruce says that he has been unable to see that these children have suffered any ill effects from this method of treatment

Of course this unorthodox type of treatment, that I have taken the liberty of denominating here the "Tolstoi" plan, has met with much opposition. In a recent critique, Ricketts (1947) made the point that while it has not been firmly established that the lax control of the disease is responsible for the degenerative complications that characterize it, there is nevertheless in existence suggestive evidence in both animals and man that this may be the case; he therefore felt strongly that in the absence of proof to the contrary it is unsound and hazardous to abandon the goal of normal glycemia in the treatment of diabetic patients Lukens' (1947) viewpoint was much the same, namely that while no single patient can be promised exemption from the severe complications of diabetes no matter how well he is treated, nevertheless after a quarter of a century of experience with insulin evidence is beginning to appear that the degree of control has an effect on some of the late complications, he therefore felt that in any case a deviation from the high standard of regulation should be made only with reluctance. Of course it is to be expected that Joslin (1947) would be in complete opposition to this new type of therapy and would remark that those who advocate free diets for children, disregarding hyperglycemia and glycosuria so long as acetonuria is absent, as yet have not published the status of their children after twenty years. Nevertheless, I am much interested in this Tolstoi plan of therapeutic approach and so are many physicians throughout the world, and by and by the twenty years will have passed

HYPERINSULINISM AND IDIOPATHIC FUNCTIONAL HYPOGLYCEMIA

The well-known reaction to the injection of an overdose of insulin in the treatment of diabetes is due to the induction by this exogenous method of a temporary state of hypoglycemia; in recent years we have come to recognize

Birmingham, Alabama, who first presented the entity in 1924, called it "hyperinsulinism," describing at the same time a state of "dysinsulinism" in which the condition of hypoglycemia was at times succeeded by a temporary one of

been reported.

this complex

rocirculatory

asthenia, cardiac neurosis, various psychoses, atypical angina pectoris and

times in adults preceding the onset of unconsciousness. Attacks frequently appear *when the blood sugar level has reached 70 mg. per 100 cc. but not* invariably; sometimes a patient will be in a serious state at 50 mg., while at another time he will have only mild symptoms or none at all at the same level.

when the blood sugar reaches as

case as either one of organic hyperinsulinism, of hypoglycemia secondary to hepatic disease, or functional hypoglycemia—at least Conn (1947), who has studied the matter for a number of years, says that over 80 per cent *of the*

causes of sponta-

eing

logic

factor, as, for example, in cases of *Addison's disease, Simmonds' disease,* severe renal glycosuria, lactation, partial or total gastrectomy and severe inanition. It therefore seems advisable to orient the therapeutic consideration toward this tri-part classification.

THERAPY

adheres to an abnormal-

are progressive in frequency and severity, (b) pre-breakfast attacks

(c) attacks occur often two to four hours after

the fasting

nt has been

eating on adequate diet; (e) the fasting blood sugar level is always depressed

preparation reveals a subnormal fasting blood sugar (a low level curve and a sharp fall to severely low levels between the second and fifth hours); and (g) the liver function is normal. The value of the dextrose tolerance test as an aid

to ingested dextrose with a high plateau diabetic type of blood sugar curve.

TABLE 16.—STANDARD PREPARATORY DIET TO PRECEDE GLUCOSE TOLERANCE TEST (CONN)
(80 gm. protein, 300 gm. carbohydrate, 2800 cals.)

Diet Plan

Breakfast.	
Fruit	1 serving
Cereal	1 serving
Bread	2 slices
Butter	1 tablespoon
Cream	½ cup
Jelly or sugar	2 tablespoons
Beverage	
Dinner:	
Meat or substitute	1 large serving
Potato or substitute	1 serving
Cooked vegetable or salad	1 serving
Bread	1 slice
Dessert	
Jelly or sugar	2 tablespoons
Butter	2 tablespoons
Cream	3 tablespoons
Beverage	
Supper.	
Meat or substitute	1 medium serving
Potato or substitute	1 serving
Cooked vegetable or salad	1 serving
Bread	2 slices
Dessert	
Jelly or sugar	2 tablespoons
Butter	2 tablespoons
Beverage	

One pint of milk daily is added to the above diet plan. Coffee and tea may be taken as desired. One ounce of sugar candy may be substituted for 2 tablespoons of sugar or jelly.

But Conn believes that the use of a standard preparatory diet will eliminate one cause for the differences obtained in different patients and indeed in the same patient. Conn's standard preparatory diet, which the patient must use for several days before the dextrose tolerance test is run, is shown in Table 16.

Complete cure often results from the removal of an adenoma. In five of Marble and McKittrick's (1940) six cases removal of a single adenoma resulted in relief of symptoms that had persisted more than four to seven years, death in the other case following seven weeks after operation had revealed an islet-cell carcinoma with multiple metastases in the liver. But several operations are often necessary to find the new growth or to locate

and remove all the new growths—witness the case of Ziskind *et al.* (1937) in which autopsy revealed an adenoma not found at two previous pancreatic resections, and that of Rayner and Rogerson (1943) in which at a second operation an adenoma was found in the head of the pancreas only after the duodenum and the head had been mobilized. Holman *et al.* (1943) reported the following bizarre occurrences: (a) a case in which the removal of one intrapancreatic adenoma failed to give relief but in which removal of a second islet adenoma in the gastrosplenic ligament produced complete cure; (b) a case of heterotopic islet adenoma of the duodenum without hypoglycemia symptoms; (c) a case of islet carcinoma apparently engrafted on a calcified islet adenoma that presumably had been responsible for hypoglycemia of varying severity during sixteen years; (d) a case of hypoglycemia in which exploration of the abdomen revealed no adenoma but isolation of the pancreas from all surrounding structures without interruption of its arterial supply resulted in apparent cure. Sometimes simply partial or subtotal pancreatectomy is resorted to but the results are often disappointing. Conn pointed to the likelihood that in the successful cases very small, perhaps only microscopic, tumors had been removed.

Patients who refuse operation can only be treated as cases of functional hypolgycemia, without much prospect of success.

Hypoglycemia in Hepatic Disease.—Conn's (1947) criteria for differentiating this from the other types of hyperinsulinism are the following: (a) the performance of liver function tests usually reveals that the function of the organ is decidedly diminished, (b) the attacks are progressive in frequency and severity, they occur most frequently between 2 and 8 A.M. before breakfast, daytime attacks are rare unless precipitated by a skipped meal, and [illegible] blood [illegible] often [illegible] ite restriction or twenty-four hour fast is always below 40 mg. per cent and often below 30 mg per cent; (e) the dextrose tolerance curve after a standard dietary preparation reveals a subnormal fasting blood sugar (hyperglycemic plateau with glycosuria and a gradual fall to hypoglycemic levels in four to seven hours). Conn believes that hypoglycemia of this type is the result of diffuse degenerative changes in the parenchyma of the liver and says that in acute degenerative lesions of toxic origin, such as in poisoning with carbon tetrachloride, cinchophen, hydrazine and smoke, the administration of large amounts of carbohydrate and protein by mouth or parenterally is indicated. In these cases if the hepatitis does not prove fatal, the hypoglycemia will have been only temporary and complete restoration of the function of the liver with respect to blood sugar regulation may be expected. If, however, there is a hypoglycemia in cases of chronic, progressive, destructive, degenerative lesions of the liver it can be controlled only by preventing long intervals without food, *i.e.*, arranging a high carbohydrate-high protein diet and including a meal before retiring at night. It is the feeling of Conn and his associates that in a small group of cases the hepatitis is due to an ascending infection of the biliary tract and that the performance of a cholecystectomy in these cases may allow sufficient restoration of hepatic function to overcome completely the hypoglycemic syndrome

Functional Hypoglycemia.—This type, which represents a disturbance in the autonomic nervous regulation of the blood sugar level, accounts for at

least 70 per cent of all cases of spontaneous hypoglycemia, a fortunate fact since these cases are controlled by dietary adjustments. Conn's (1947) criteria for differential diagnosis here are the following: (a) the malady is not progressive in severity, the attacks occur most frequently when the patient is under emotional or physical tension and are relieved by vacations, etc, they occur two to four hours after meals, and there are no pre-breakfast attacks and no effects of skipped or late breakfast, (b) the liver function is normal; (c) the fasting blood sugar in a patient on adequate diet is normal and it is also normal after a period of carbohydrate restriction or a twenty-four hour fast; (d) the dextrose tolerance curve after a standard dietary preparation reveals a normal fasting blood sugar (sharp fall to hypoglycemic levels between second and fourth hour) Conn says that he has come to regard patients with functional hypoglycemia as belonging to the group who react excessively not only to the insulogenic stimulus but to most physiologic stimuli, *i e.*, that in short they are persons with an instability of the autonomic nervous system; they are as a group extremely conscientious, they shoulder responsibilities well but fret about them and react intensely to minor disappointments, and they often suffer from vasomotor instability and gastric hyperacidity. While the presumptive evidence of a psychosomatic disturbance in these individuals is very strong, it is nevertheless an incontrovertible fact that the hypoglycemia that often produces their most troublesome symptoms can be well controlled by dietary means.

In the beginning of the study of this disease patients were put on high carbohydrate diets, but soon it was realized that these diets very frequently resulted in an increased number of attacks, the large amounts of carbohydrate ingested affording an added stimulus to insulogenesis with a resultant quick slide into hypoglycemia. The first definite advance in treatment consisted in the use of a diet low in carbohydrate, high in fats, normal or slightly below normal in proteins, and frequent feedings. The next advance consisted in the substitution of a high protein for a high fat diet by Conn, who justified his diet upon the following basis (a) although protein during its metabolism yields about 50 per cent of its weight as dextrose, the process of glyconeogenesis from protein proceeds at a slow and even rate and therefore results in no elevation of blood sugar and consequently no secondary fall, and (b) the long period required for the absorption of protein and its conversion to dextrose affords a steady supply of dextrose over a prolonged period of time Conn's (1947) recommended diet, which is apparently the one most often employed in treatment of these cases nowadays, contains from 120 to 140 gm of protein, from 50 to 100 gm. of carbohydrate, and the remainde fats in order to make up the necessary calories for maintenance. It is give as three meals a day with the occasional addition of a "protein meal" bedtime.

Drugs —*Epinephrine* (*adrenalin*), in the usual dose of 0 5 to 1 cc. of 1.1000 solution, is used to rouse the patient from a severe attack. Conn (19 found that supplementing the high protein dietary regime with subcutane injections of small amounts of the drug twice daily sometimes satisfacto kept the blood sugar above the attack level and did so without increasing oxidation of carbohydrate. He thought it likely that "slow epinephrine" Asthma) might be a valuable adjunct to therapy in some cases. *Ephedrin* been used only with doubtful results so far. *Pituitrin*, in injections of 0 5 cc , is sometimes effective in emergencies, as is also *caffeine* in the fo

caffeine sodiobenzoate, 5 grains (0.3 gm.) or more. Harris says that a cup of coffee or a glass of Coca-Cola is so effective as to serve in some instances as a diagnostic test. Allan proposed the use of *thyroid substance* as in myxedema, but after several years' trial he stated, in 1935, that he felt it did not give substantial results. John (1935) felt that in functional cases if *insulin* is given [illegible]

helpful in doses of 1½ grains (0.1 gm.) night and morning in cases difficult to control or in patients who will not adhere to the diet; *bromides* are also effective, it seems, but he counsels against their employment because of bromism. Portis and Zitman (1943) had good results in the injection of atropine in a small number of cases in which hypoglycemia was associated with fatigue in neuropsychiatric patients, their feeling being that perhaps the hyperinsulinism was the result of stimulation of the right vagus nerve resulting from emotional processes relayed through the hypothalamus to the autonomic nervous system; however, Karlan and Cohn (1946) did not find atropine beneficial in their cases. Sometimes in emergencies the intravenous injection of *dextrose* must be resorted to: 10 gm. in 50 to 100 cc. of sterile physiologic salt solution, or, as preferred by some men, a smaller amount of a more concentrated solution.

DIABETES INSIPIDUS

Diabetes insipidus is a disease characterized by the excretion of quite enormous amounts of urine and a resultant loss of tissue fluids that has to be compensated by the ingestion of equal quantities of water. The urine is practically colorless, does not contain sugar, is of very low *specific gravity*, and contains none of the elements suggestive of renal involvement. There is a decrease in the flow of saliva, the mucus becomes thick and tenacious, there is constipation, practically no sweating, and the skin becomes very harsh and dry. The patients are made very miserable by the necessity to urinate so often and to be constantly drinking water. This excessive water drinking usually causes the appetite to become abnormal because of the [illegible] to bring all the water to body [illegible] water will be taken, there *is* [illegible] and tremor. The disease may occur at any age but is [illegible] many cases have been [illegible] instances it has been [illegible] at the Mayo Clinic i[illegible] refrain from drinking any fluids for as long a period as he can without extreme discomfort, and then a specimen of urine is obtained; in twenty-nine of their thirty-four cases the specific gravity of this specimen was less than 1.010, and in four of the other five cases it was 1.011.

Cranial injuries, brain tumors, encephalitis and other diseases of the central nervous system (especially syphilis), abdominal aneurysm, tuberculous peritonitis, and other disturbances have been associated with diabetes insipidus a number of times, but in many cases it is not possible to trace a

connection of this sort. It would seem that in this disease the pituitary body is at fault through failure to supply a necessary hormone from its posterior portion, but at present we have little more precise information than this fact. There is now conclusive evidence that the disease also exists in an heredi- [illegible]

Diabetes insipidus was described by Johann Peter Frank, in 1794. Cushing and his coworkers first drew attention to the apparent hypophyseal relationship in 1912.

THERAPY

Pituitrin.—In the vast majority of cases hypodermic injections of pituitrin control the symptoms of this disease; that is to say, the polyuria ceases or is very markedly reduced and there is then a corresponding decrease in the craving for water The dose necessary to accomplish relief is usually 1 cc. of obstetrical pituitrin, or of pitressin, but the duration of the relief varies from four to forty-eight hours, in sixteen of a series of twenty-six cases reported by Rowntree, it was twenty-four hours at least. Most patients prefer to take the injection at night in order to have their greatest period of freedom during the sleeping hours, for the necessity to be urinating frequently throughout the night is one of the most distressing features of the disease. Since peristalsis is sometimes markedly increased by pituitrin, it is advisable to have the injection taken about two hours before bedtime in order to permit a visit to the stool before retiring The continued use of the drug over a long period of time gives rise to no serious untoward effects; however, it may be wise to counsel cessation of water ingestion very soon after taking the injection, for with a sudden decrease in water elimination there is some danger of water "intoxication" if fluid continues to be poured into the system.

Blumgart reported a series of cases in which intranasal application of the pituitrin was fully as satisfactory as subcutaneous injection. From 0 5 to 5 cc. of obstetrical pituitrin was sprayed into the nose every three to four hours, [illegible]

to the nasal mucosa by means of the fingertip Extract incorporated in jelly was found to be less effective and more expensive. Smith had 40 to 50 mg. of the powder blown up into the nose from a powder blower, Marble used this method also, it being much cheaper than any of the others, but one of his patients successfully took the powder in the old-fashioned method of taking snuff, as did Canelo and Lasser's patient also Greene and January (1940), Blotner (1942), Court and Taylor (1943) and Jones (1944) reported the satisfactory intramuscular injection of a suspension of pitressin tannate in oil, the duration of action of an injection in Blotner's seven cases of idiopathic origin was forty-eight to sixty hours and in the one case in which the syndrome resulted from brain tumor the duration was thirty hours; the usual dose of this preparation is 1 cc

Miscellaneous Measures.—Scherf (1932) reported five cases treated with large doses (30 grains, 2 gm. daily for five days) of amidopyrine (pyramidon), in

four of which marked diminution in symptoms was induced. The effect was of only short duration but could be obtained again after a short interruption of the treatment; the effectiveness of pituitrin was not altered by changing for a while to amidopyrine. De Gowin (1935) *confirmed the efficacy of this drug;* however, because of its tendency to cause agranulocytosis, it should be used only under hematologic control.

Treatment of associated diseases, such as syphilis, is of course indicated and will nearly always result in an improvement in the general health; such measures alone rarely bring about any reduction in the polyuria, however. Surgical removal of associated tumors has sometimes corrected the condition. Rowntree *said "Spinal puncture is a desirable procedure in all cases, unless* contraindicated by the presence of an intracranial neoplasm," though it is not apparent in the record that it was worth much in his series of cases; cures have followed upon this procedure, but it is well to bear in mind that spontaneous cure is not unknown in this unique disease.

It is usually the practice to reduce the patient's intake of sodium chloride to the practically irreducible minimum, a measure which in itself is often very helpful. Beaser (1947) felt that maximum restriction of both salt and protein is necessary in order to attain maximum therapeutic benefit from pituitrin, no *matter how the latter is administered. In confirmation of earlier experimental* findings, Peters (1944) reported a case in which the polyuria was suppressed by [illegible]

tw [illegible]

effective in reducing urine output than a low salt diet but it did increase the *patient's responsiveness* to pitressin and diminish his diuretic response to sodium chloride.

Weinstein and Spingarn (1940) reported a case following, and presumably incited by, a middle ear infection, which terminated after deep roentgen therapy to the pituitary region.

DISTURBANCES IN MENSTRUATION

AMENORRHEA, HYPOMENORRHEA, OLIGOMENORRHEA AND DELAYED MENSTRUATION

The first of these terms means absence of menstruation, the second scanty menstruation, the third infrequent menstruation, and the fourth what the term implies. Other than menopause, of which it is one of the signs, the most frequent cause of amenorrhea is of course pregnancy and the height of lactation. Other very simple things may bring about these disturbances, especially in girls and younger women, such as change in climate or environment, a love

tuberculosis, diabetes mellitus, the deficiency and hematologic disturbances In several psychoneurotic maladies, especially anorexia nervosa, these disturb-

ovarian and anterior pituitary hormonal imbalances is nowadays accepted teaching, but the true hormonal regulation of bleeding has not yet been completely elucidated Of course pelvic tumors, malformations, or inflammatory disturbances can appear in the causative role

THERAPY

Actually, the mere absence of menstruation is in itself nothing to be greatly agitated about Oftentimes the beginning of satisfactory sexual life establishes or reestablishes the flow, but many women have gone into marriage while amenorrheic and have become pregnant all the same However, the occurrence

primary disturbance. Otherwise, that is to say if all examinations reveal a completely healthy woman who simply is not menstruating often enough or

struate after the use of this drug, pregnancy may be diagnosed as accurately as with the *Friedman test*; Winter (1940) could not confirm this position since the test failed in one of his four cases; however, it succeeded in the six cases of Cherniack and Sheps (1941) and in 94.5 per cent of the ninety cases of Friedmann (1944).

As to therapy with the sex hormones, the following is the plan suggested by Smith (1944), Professor of Gynecology at the Harvard Medical School: give

the twenty-eighth day. The last two steps are repeated twice, and then again twice, but reducing the diethylstilbestrol to 0.3 mg. daily. After the next period, the usual course of diethylstilbestrol is given daily but the progesterone

above schedule of treatment no spontaneity of flow is discernible it is reasonable to assume that the patient has some basic irremediable defect and that

rhea is not based on sound physiologic principles, since the amenorrhea usually

ing cessation of treatment, (b) Abarbanel *et al.* (1943) felt that the principal indicatio

maladjus

origin a

thyroid over the space of many months was of much greater importance, (c) Novak (1943) *felt that the inadequacies of diethylstilbestrol in the treatment* of amenorrhea need to be stressed. As for progesterone, normal menstrual cycles followed for a variable period of time in only one-third of Allen and Soule's (1943) twenty-three cases, Rakoff (1946) *said that his studies of* high dosage provided no answer but just raised many more questions; and Hamblen kindly informed me, in early 1947, that he still felt, as he had in 1942, that the therapeutic role of progesterone was yet to be delineated clearly.

Reidenberg (1943) said that restoration of normal menstrual function occurred in 71 per cent of fifty-one amenorrheal women and in 78 per cent of thirty-seven oligomenorrheal women following low dosage *irradiations* of the pituitary gland and the ovaries. Randall (1947) said it had been found

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a lowered rate of metabolism is found in patients selected for this therapy they elevate the rate by the use of thyroid before the roentgen treatment and that when the menses reappear estrogens are administered cyclically.

MENORRHAGIA AND METRORRHAGIA

(Dysfunctional Uterine Bleeding)

The first of these terms means prolonged or profuse flow, and the second, flow at irregular intervals between the periods, but they can probably be satisfactorily designated here by the single term, excessive bleeding. Sometimes such bleeding occurs just as a girl reaches maturity and does not recur, but it may take place at any time during, or even after, a woman's menstrual life. In most of the latter, postmenopausal, instances the cause is a neoplastic

uterine fibroids or polyps, endometrial hyperplasia, pelvic inflammatory disease. Excessive bleeding may occur in either hypo- or hyperthyroidism and is seen in some of the other classical endocrinopathies. Likewise it probably occurs as a reflection of some of the less understood pituitary-ovarian im-

THERAPY

their first few periods, rest in bed, an ice-bag to the lower abdomen, and ergot are time-tried remedies. The last is probably more successful since ergonovine

rhagia and six of their seven with menorrhagia. Smith (1941) said that doses approaching tolerance may sometimes have to be given. It is rare for a patient who is not a youngster to escape successive dilatation-curettages. The men of my time in hospital were given to understand that a diagnostic curettage is one thing and a therapeutic one quite another, but attitudes

Harvard Medical School, advised as follows: To those who bleed regularly but too profusely or too long, give 10 mg. of progesterone and 1 mg. of estradiol intramuscularly on the twenty-first day and follow on the twenty-second to the twenty-fifth day by 10 mg. of progesterone intramuscularly; three cycles of this therapy are usually sufficient. For those whose periods are occurring too frequently the same procedure is used, beginning the injections eight days before the anticipated onset of flow and continuing until the cycle lengthens. For those having continuous flowing, Smith advised the immediate intramuscular injection of 10 mg. of progesterone and 1 mg. of estradiol and then of 10 mg. of progesterone daily for the next four days. He said that during this time the bleeding will probably decrease or cease and that two to four days later a fairly normal period will occur. Counting the beginning of this period as the first day, he would have the injections repeated beginning on the twenty-first day. Treatment of this sort he said should be given at least twice and that it may be required again after a lapse; if the patient is bleeding profusely, the daily dose of progesterone may even be raised to 50 mg. for a time. Cuyler, Hamblen and Davis (1942) employ diethylstilbestrol by mouth in daily doses ranging from 2 to 6 mg. in place of the estradiol; others have since used diethylstilbestrol with satisfaction. Hamblen (1947) said that in his opinion therapy of this cyclic estrogen-progesterone type renders useless and unnecessary repeated curettages, radium or roentgen ray therapy and hysterectomy. Rubenstein (1943) felt that cases could be separated into two groups by employment of the vaginal smear technic, progesterone being given to those in whom a highly cornified vaginal smear indicates hyperplastic endometrium and estrogen to those [illegible] Testosterone seems [illegible]

the development of male characteristics, hirsutism, atrophy of the [illegible] and change of voice. Karnaky (1943) observed a case in which these changes were not reversed upon the cessation of treatment.

Low dosage irradiation of the pituitary gland and ovaries was successfully employed in about half of Reidenberg's (1943) thirty-seven cases; however, [illegible] of a young woman who became pregnant and [illegible] nic and pituitary [illegible] tment is entirely [illegible] e had seen some tragic permanent amenorrheas caused in young women in this way and that he does not use irradiation in women under thirty-five years of age.

Biskind *et al* (1944) said that evidences of nutritional deficiency are to be [illegible] patients and that prompt improvement [illegible] vitamin [illegible] mployed vitamin K in an attempt to stop the excessive bleeding in the [illegible] lief that impaired hepatic function is a contributory factor in the genesis of various menstrual disorders. It seems to me that it will not be easy to convince the gynecologists that simple vitamin replacement therapy will be effective in many cases of menorrhagia or metrorrhagia.

ESSENTIAL DYSMENORRHEA

(*Painful Menstruation*)

Perhaps more than 50 per cent of women suffer from dysmenorrhea, the symptoms varying from a mild physical and mental discomfort to severe attacks of pain that wrack the patient's back, head, legs and lower abdomen for several days and leave her in a state of great fatigue during the early part of the intermenstrual period. Grant that dysmenorrhea is only a symptom and not a disease, and classify the various types on an alleged causative basis, the fact will remain that there is a constitutional something underlying all the cases; that is to say, that the dysmenorrheic woman differs in some essential way from the nondysmenorrheic. This position is of course challenged, and the attempt is made to find a neuralgic, ovarian, congestive, obstructive, inflammatory, mechanical, autonomic, endocrine, or allergic cause in all cases—which would be very fine were it not for the fact that the very same *causes* are found in many women who do not have dysmenorrhea. Therefore, in the present state of our knowledge, the term "essential dysmenorrhea" would seem still to be permissible.

THERAPY

Surgical Measures.—Various surgical measures from bilateral ovarian denervation or presacral neurectomy to hysterectomy are employed, of which perhaps the soundest theoretically is dilatation of the cervix in the attempt to convert the nulliparous uterus into a condition similar to that of the parous uterus, it being noteworthy that women who have suffered from dysmenorrhea frequently no longer do so after they have borne a child. This dilatation, however, oftentimes gives only temporary relief, in which cases the use of pessaries is advised in the hope of prolonging the asymptomatic period—a practice that many physicians look upon as vicious. It is also claimed that if the internal os is severed in addition to the dilatation, the percentage of permanent cures is greatly increased. [illegible]

have employed it have found it effective.

I believe that all but a relatively few enthusiastic gynecologists have given up the routine suspension of retroverted uteri, a truly heinous anatomical abnormality that has at one time or another been held responsible for all of the ailments of the daughters of Eve.

Exercise.—Muller, in 1934, seemed to have convinced himself by careful [illegible]

healthy.)

Hygiene.—There is no reason why the patient should not bathe as usual except that the tub bath may be esthetically objectionable. The shower or sponge bath is still available, however, and if taken quite hot is often very helpful.

Harvard Medical School, advised as follows: To those who bleed regularly but too profusely or too long, give 10 mg. of progesterone and 1 mg. of estradiol intramuscularly on the twenty-first day and follow on the twenty-second to the twenty-fifth day by 10 mg. of progesterone intramuscularly; three cycles of this therapy are usually sufficient. For those whose periods are occurring too frequently the same procedure is used, beginning the injections eight days before the anticipated onset of flow and continuing until the cycle lengthens. For those having continuous flowing, Smith advised the immediate intramuscular injection of 10 mg. of progesterone and 1 mg. of estradiol and then of 10 mg. of progesterone daily for the next four days He said that during this time the bleeding will probably decrease or cease and that two to four days later a fairly normal period will occur. Counting the beginning of this period as the first day, he would have the injections repeated beginning on the twenty-first day. Treatment of this sort he said should be given at least twice and that it may be required again after a lapse; if the patient is bleeding profusely, the daily dose of progesterone may even be raised to 50 mg. for a time. Cuyler, Hamblen and Davis (1942) employ diethylstilbestrol by mouth in daily doses ranging from 2 to 6 mg. in place of the estradiol, others have since used diethylstilbestrol with satisfaction. Hamblen (1947) said that in his opinion therapy of this cyclic estrogen-progesterone type renders useless and unnecessary repeated curettages, radium or roentgen ray therapy and hysterectomy. Rubenstein (1943) felt that cases could be separated into two groups by employment of the vaginal smear technic, progesterone being given to those in whom a highly cornified vaginal smear indicates hyperplastic endometrium and estrogen to those whose smear resembles that of a normal prepubertal girl. Testosterone seems in many instances undoubtedly capable of checking dysfunctional bleeding, but most observers feel that its use is contraindicated since it may lead to the development of male characteristics, hirsutism, atrophy of the breast and change of voice. Karnaky (1943) observed a case in which these changes were not reversed upon the cessation of treatment.

Low dosage irradiation of the pituitary gland and ovaries was successfully employed in about half of Reidenberg's (1943) thirty-seven cases; howev despite Kaplan's (1943) report of a young woman who became pregnant a gave birth to a normal child after roentgen therapy of the splenic and pituitar regions, many men do not feel certain that this type of treatment is entirel safe—Te Linde, in discussing Kaplan's paper, said that he had seen some tragic permanent amenorrheas caused in young women in this way and that he does not use irradiation in women under thirty-five years of age.

Biskind *et al.* (1944) said that evidences of nutritional deficiency are to be found in a large proportion of these patients and that prompt improvement in the gynecologic condition often follows upon the administration of vitamin B complex orally or parenterally. Gubner and Ungerleider (1944) employed vitamin K in an attempt to stop the excessive bleeding in the belief that impaired hepatic function is a contributory factor in the genesis of various menstrual disorders. It seems to me that it will not be easy to convince the gynecologists that simple vitamin replacement therapy will be effective in many cases of menorrhagia or metrorrhagia

ESSENTIAL DYSMENORRHEA

(Painful Menstruation)

Perhaps more than 50 per cent of women suffer from dysmenorrhea, the symptoms varying from a mild physical and mental discomfort to severe attacks of pain that wrack the patient's back, head, legs and lower abdomen for several days and leave her in a state of great fatigue during the early part of the intermenstrual period. Grant that dysmenorrhea is only a symptom and

attempt is made to find a neuralgic, ovarian, congestive, obstructive, inflammatory, mechanical, autonomic, endocrine, or allergic cause in all cases—which would be very fine were it not for the fact that the very same *causes* are found in many women who do not have dysmenorrhea. Therefore, in the present state of our knowledge, the term "essential dysmenorrhea" would seem still to be permissible.

THERAPY

Surgical Measures.—Various surgical measures from bilateral ovarian denervation or presacral neurectomy to hysterectomy are employed, of which perhaps the soundest theoretically is dilatation of the cervix in the attempt to convert the nulliparous uterus into a condition similar to that of the parous uterus, it being noteworthy that women who have suffered from dysmenorrhea frequently no longer do so after they have borne a child. This dilatation, however, oftentimes gives only temporary relief, in which cases the use of pessaries is advised in the hope of prolonging the asymptomatic period—a practice that many physicians look upon as vicious. It is also claimed that if the internal os is severed in addition to the dilatation, the percentage

insufflation of the fallopian tubes has been advocated, but not all of those who have employed it have found it effective.

I believe that all but a relatively few enthusiastic gynecologists have given up the routine suspension of retroverted uteri, a truly heinous anatomical abnormality that has at one time or another been held responsible for all of the ailments of the daughters of Eve.

Exercise.—Miller, in 1934, seemed to have convinced himself by careful

healthy.)

Hygiene.—There is no reason why the patient should not bathe as usual except that the tub bath may be esthetically objectionable. The shower or sponge bath is still available, however, and if taken quite hot is often very helpful.

Psychotherapy.—There is little to say about this save that, as recently developed by Hunter and Rolf (1947), there is often a psychosomatic aspect to dysmenorrhea and that the psychotherapeutic approach is frequently the rational and rewarding one. It should be made plain that Hunter and Rolf's belief was that the neurosis in these instances is initiated and developed by physiologic changes rather than by suppression or repression of psychic

as readily. Hunter and Rolf found that some dramatic procedure performed with confidence is necessary to affect the average patient and that if, by psychoanalysis, *the patient can be made to believe that the cause has been* removed the pain threshold is elevated and the symptoms relieved.

TABLE 17.—EXERCISES FOR HEALTHY DYSMENORRHEIC WOMEN (CLOW)

1. *Floor Polishing.* Kneel on "all fours." Swing right arm with elbow stiff, through a semicircle, as if polishing the floor, reaching as far forward and as far back as possible. Repeat swing ten times with each arm
2. (a) *Bending.* Stand with feet apart. Stretch arms above head, bend forward and touch ground

   (b

   (c) *Swaying* Stand with feet apart Stretch arms above head Sway body and arms to right then left. Repeat slowly ten times
3. "*Rowing*" Sit on floor with knees straight and feet pressed against wall Lean forward and touch wall with knuckles, allowing knees to bend slightly. Repeat rhythmically twenty times.

times each side.

6. *Bean Picking* Throw 20 small objects, such as beans, on the floor Pick up one at a time and place on a shelf above the head using hands alternately. Do it as quickly as possible

Sedatives, Analgesics and Antispasmodics.—It is the rare and fortunate patient who responds to the sedatives alone; these drugs are discussed under Insomnia. Likewise, it is unusual for a patient with severe dysmenorrhea to obtain complete relief from analgesics, but many patients do have the worst edge taken off their pain by them. Those most frequently used are acetanilid, 3 grains (0 2 gm.), acetphenetidin, 5 grains (0.3 gm.), and acetylsalicylic acid, 5 grains (0.3 gm); caffeine citrate, 2 grains (0.12 gm.), combined with any one

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Alcohol is the analgesic par excellence in dysmenorrhea, as many patients know without being so instructed by the physician. I believe that there are plenty of women capable of taking alcohol in small amounts and at long intervals as a medicine. That the gynecologist fears this type of therapy more

than does the general practitioner is probably due to the fact that the gynecologist, like all other specialists, knows his patient too little to have a valid opinion of her stability.

Opium will of course relieve this pain, but its use is very dangerous because of the great likelihood of inducing the habit. There are some cases, however, in which respite can be obtained by no other agent. Codeine is preferable to morphine or dilaudid; the ½-grain (30 mg.) dose twice a day, or the ¼-grain (15 mg) dose at shorter intervals, is less completely analgesic than the stronger drugs but it is also less constipative, less nauseant and less depressant to the general metabolism. The danger of codeine habituation is practically nil.

In the experience of most physicians who use atropine or some other member of the belladonna series—and nearly all do, for there is occasionally a strikingly good result—the colicky pains are much more relieved than are the backache, bearing down in the lower abdomen, lassitude, etc. The following prescription combines a sedative, ½ grain (30 mg.) of phenobarbital, a member of the belladonna group of antispasmodics, extract of hyoscyamus, ⅚ grain (50 mg.) and an analgesic, acetanilid, 3 grains (0.2 gm); the patient should begin the use of these capsules one day before the onset of the period is expected

℞	Phenobarbital	gr vi	0 4
	Extract of hyoscyamus	gr vi	0 4
	Acetanilid	gr. xxxvi	2.3

Make 12 capsules
Label 1 capsule every four hours Not to exceed 4 doses daily

Davis (1941) stated that the following drugs are employed in mixture at the Chicago Lying-In Hospital camphor monobromate, ½ grain (30 mg.), atropine sulfate, 1/500 grain (0.12 mg.), papaverine hydrochloride, ¼ grain (15 mg); phenacetin, 3 grains (0 2 gm.); acetylsalicylic acid, 3 grains (0 2 gm.) One might write such a prescription as the following

℞	Camphor monobromate	gr vi	0 4
	Atropine sulfate	gr. 1/40	0 0015
	Papaverine hydrochloride	gr iii	0 2
	Acetphenetidin (phenacetin)	gr. xxxvi	2 3
	Acetylsalicylic acid (aspirin)	gr xxxvi	2 3

Make 12 capsules
Label· 1 capsule every four hours Not to exceed 4 doses daily

[illegible]

occasionally also arrhythmias are induced or accentuated.

Weinberg (1945) reported good results from the employment of 2-grain (0 12 gm.) pavatrine tablets, one to be taken three times a day after meals beginning three days before the onset of the expected period and likewise on the first day of the period, the medication being continued one or two days if the period is delayed.

Thyroid Substance.—This agent, used as in hypothyroidism, is frequently helpful; in Shute's (1940) series of 130 cases it was effective far more often than any other agent or measure, bringing about "cure" in fifty-eight cases One should not be reckless in the use of thyroid substance, however, because dysmenorrhea is not unknown in patients with a slight hyperthyroid tendency and there exists at least the theoretical possibility of exaggerating this state.

Sex Hormones.—Smith (1944) of Harvard, whose recommendations for sex hormone therapy in other menstrual disturbances I have freely cited, offered a program of treatment for dysmenorrhea, too, but I think it significant that he prefaced it by saying that temporary relief has been obtained with trials of all the available sex hormones with results that have been unpredictable and not consistently confirmable. Hirst *et al.* (1942), of Hamblen's group at Duke, employed estrogenic therapy and obtained a complete absence of pain in 25 per cent and marked relief in 60 per cent of the cycles studied, and after cessation of therapy there was complete absence in 5 per cent and marked relief in 28 per cent of the cycles studied. These results do not seem very impressive to me considering the variability of the phenomena in dysmenorrhea. Randall and Odell (1943) said that in their opinion the use of estrogens may possibly be dangerous.

Harding (1945) reported favorably upon the use of one of the progesterone series of agents. The use of testosterone has been favorably reported a number of times; Jacoby and Rabbiner (1943) obtained relief in four and improvement in eight of their eighteen patients, but this is considered by many observers to be a dangerous agent to use (see Menorrhagia).

PERIODIC INTERMENSTRUAL PAIN

Some women experience discomfort, malaise and uni- or bilateral intermit- [illegible]

distention or rupture of an ovarian cyst. The whole operative gamut has been run in these cases, but it is difficult to see how any therapy, other than the use of sedatives and analgesics if necessary, could be really justified in the present state of our knowledge. However, there do not lack men who would have testosterone used in these cases; this is certainly not conservative therapy. Smith (1944) said that thyroid substance is the simplest medication; it is certainly the safest.

PREMENSTRUAL TENSION

Several years ago Frank used the term "premenstrual tension" to describe a syndrome occurring in the premenstrual phase a week or so preceding the menstrual flow and terminating sharply with the appearance of that flow. The [illegible] symptoms are headache, emotional instability, irritability, abdom- [illegible] tus and swell- [illegible] in degree and [illegible] for the family the psychic alterations in particular may pose [illegible] of the sufferer.

THERAPY

Greenhill and Freed (1941) approached this malady as a disturbance in electrolyte and water balance and treated it with ammonium chloride to prevent the retention of sodium in the tissues. The drug was given in 15 grain (1 gm) doses three times daily, starting ten to twelve days before the expected period, and the patient was asked to refrain from using table salt or sodium bicarbonate preparations during the treatment. Definite relief was obtained in thirty-four of the forty patients.

Rubenstein (1942) reported six interesting cases in which the principal [illegible]

each of these cases when 1 mg. of estradiol was injected intramuscularly about a week before the onset of menstruation Smith (1944) indicated that he uses 0.2 to 0.3 mg. of diethylstilbestrol orally with breakfast daily throughout the cycle in cases of premenstrual tension; Rubenstein (1942) used this agent in somewhat smaller dosage successfully in some of his cases.

Freed (1945) found that most of his group of sixty patients obtained definite relief following treatment with testosterone. Thirty of the patients received injections of 10 to 25 mg. of testosterone propionate, depending upon the severity of the symptoms, on the tenth and third days preceding the expected menses; the other thirty were given methyl testosterone by mouth in 10 mg. dosage daily starting ten to seven days before the expected onset. It was thought that the oral therapy was more effective than the parenteral, in one patient given the drug by mouth nausea was experienced, and in those who received it parenterally menstruation was occasionally delayed but otherwise there were no untoward reactions. However, testosterone is a potentially dangerous agent (see Menorrhagia)

Biskind *et al.* (1944) said that in some instances they effected relief of their patients through administration of the vitamin B complex.

PERIODIC MASTALGIA

The fact that in some instances of premenstrual tension the only disturbing symptom has been painful breasts during the premenstruum has led some observers to classify this condition as a separate entity. Smith (1944) said that the simplest remedy in these cases is diethylstilbestrol, 0.3 mg. daily, reduced to 0.2 mg daily as soon as relief is experienced, but he most emphatically warned that such therapy is to be restricted to those whose breasts are engorged, thickened or diffusely nodular, the presence of a discrete mass, cystic disease, or bloody secretion of course calling for thorough study of the local situation However, Fluhmann (1944) advised that judgment be reserved v

following

from the

been used in some of these cases of mastalgia, but again it seems necessary to repeat that most men do not look upon the use of this agent as a conservative measure.

THE MENOPAUSE

At the period in their lives when involution of the ovaries takes place, which occurs usually between the forty-fifth and fiftieth years women ... the climacteric state, of

per cent of women the only other symptom noted is slight "flushing." But in the remaining 80 per cent one or more of the following are experienced in variable degree: hot flushes, characterized by sudden dilatation of the skin vessels, sweating, and a sensation of suffocation often succeeded by a feeling of cold; precordial pain, palpitation, and high blood pressure; arthritic pains; paresthesias, tinnitus, vertigo, headache, insomnia; emotional instability, mental clumsiness, hypochondriasis and depression with suicidal tendency.

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This is not a disease but rather a natural transition in her life which every woman must experience. As a matter of fact, as Novak (1940) pointed out, there are not a few women to whom the climacteric comes as sort of boon, women who are transformed from a thin scrawny state after years of child-bearing and domestic worry into a plumper, serene type of matron, a sort of second flowering. To be sure, some are disturbed much more than others and really suffer severe physical discomfort and mental disquiet, but we in medicine have as yet no magic wands at whose waving these things are invariably caused to pass. In the vast majority of instances with a moderate amount of disturbance, the sedatives remain the best drugs; Buxton (1944) reported that almost half of the eighty patients in his series were relieved by phenobarbital alone. Thyroid extract is of value in patients tending toward the hypothyroid state. Sympathetic and understanding treatment in her home is to be fostered for the patient by acquainting the family with the nature of the disturbances and the extent to which their helpfulness will be of real assistance to her. A hobby, or anything that will prevent introspection, is to be encouraged Travel, if it can be afforded, is sometimes desirable, but on the other hand it may be harmful to a woman who will worry over the conduct of her home while she is away. The fear of cancer should be dispelled, by repeated examinations if necessary. Under the head of "estrogen therapy" below, I have attempted to present what may be currently expected from this type of treatment.

Estrogen Therapy.—*Indications and Results.*—Of course those who are making a special study of sex hormone therapy in the menopause are justifiably using these preparations a great deal, but for the general practitioner the fact ... omen ... con-

sult a physician there is a large proportion who are not likely to profit by estrogen therapy. For example, of 100 women admitted to the Boston Dispensary endocrine clinic because of severe menopausal symptoms, Lawrence and Moulyn (1941) found a positive test for prolan in the urine in only forty-eight In 81 per cent of this positive group the symptoms were preponderantly

those of vasomotor instability, which was, to be sure, definitely benefited by estrogen therapy in 90 per cent of instances. However, in the other fifty-two patients, whose test for urine prolan was negative, treatment with these preparations caused improvement in only 25 per cent, whereas simple psychotherapy or sedation brought relief in over 80 per cent. Abarbanel *et al.* (1943) also controlled about 50 per cent of their more than 400 menopausal patients without resort to estrogen therapy.

The classical peripheral circulatory changes, the hot flushes, headaches, asthenia and insomnia, seem to be the symptoms favorably affected with greatest regularity. Shorr (1945), who has contributed much toward the devel-

symptoms as not part of the menopausal syndrome but of a different nature, on the other hand, when failure to relieve symptoms is due to inadequate dosage of estrogen the vaginal smear provides the simplest method of insuring that the dosage requirements of the individual patient are met. Sevringhaus (1941) pointed out, however, that with regard to symptomatic response as a whole there are often variations in the results from day to day in a given patient. Observers disagree regarding the effect upon hypertension; Shorr, however, found that well stabilized hypertensions were scarcely or not at all affected in his series but those associated with emotional instability tended to stabilize at lower levels under estrogen therapy. Apparently some slight increase in libido is hoped for more often than it is achieved. The arthralgias may persist very severely despite most intensive estrogen treatment. Cohen

atric disorder in its definition.

Choice of Preparation—I believe it is the consensus that equivalent results can be obtained with all of the estrogenic preparations provided suitable dosage adjustment is made. However, diethylstilbestrol has been by far the most extensively employed of these agents because of its relative cheapness and greater degree of effectiveness when given by the convenient oral route.

Dosage.—The wide variations in response from patient to patient, above discussed, together with the fact that there is as yet no general agreement as to what amount of symptomatic relief should really be sought, make it at present impossible to state anything like a standardized dosage of these preparations, particularly the natural estrogens However, as regards diethylstilbestrol, there seems now to be general agreement with Novak's (1944) statement that only rarely is a larger daily dose than 0.1 mg needed. Abarbanel *et al* (1943), as the result of an experience in a large number of patients, ad-

THERAPY

Table 18.—Reduction Diets as Used by Newburgh

Four Hundred and Fifty Calorie Diet

Protein 60 gm., Fat 9 gm. and Carbohydrate 32 gm.

	Household Measure	Weight, Gm
Breakfast:		
6 per cent fruit	1 serving	100
Skimmed milk	1 glass	200
Coffee..		Ad libitum
Luncheon:		
Meat or fish	2 oz	60 cooked
3 per cent vegetable	1 serving	100
Skimmed milk	½ glass	100
Dinner.		
Meat or fish	3 oz	90 cooked
3 per cent vegetable	1 serving	100
Skimmed milk	½ glass	100

Six Hundred Calorie Diet

Protein 65 gm., Fat 9 gm and Carbohydrate 65 gm.

Breakfast.		
6 per cent fruit	1 serving	100
Bread.. .	1 slice	30
Skimmed milk	½ glass	100
Coffee .		Ad libitum
Luncheon:		
Meat or fish	2 oz.	60 cooked
3 per cent vegetable ..	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Skimmed milk.	1 glass	200
Dinner:		
Meat or fish .	3 oz.	90 cooked
3 per cent vegetables		
1 raw..	1 serving	100
1 cooked...	1 serving	100
9 per cent fruit or vegetable	1 serving	100
Whole milk.	½ glass	100
Tea or coffee		Ad libitum

off the surplus in storage. Starvation would be the ideal but for the fact that under such conditions there occurs depression of metabolic activities sufficient to defeat our purpose. The treatment must therefore consist in supplying what one might call a small air draft of food in order to keep the fat fire in a good glow of burning.

Newburgh's Diet.—The feeling has been growing through recent years that attempts to accomplish a slow loss of weight through rather liberal plans of dieting, which have been in vogue in many clinics, have for the most part *failed because the patients are so discouraged with the slow loss of weight that*

they give up the attempt altogether. The tendency nowadays therefore is to revert to dietaries in which the calories are very sharply restricted, and there is no longer any fear that patients on these radical reduction diets will not maintain nitrogen balance, for Strang and McClugage showed a good many

TABLE 18—*Continued*

Eight Hundred Calorie Diet

Protein 73 gm, Fat 28 gm and Carbohydrate 65 gm

Breakfast:		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Luncheon		
Meat or fish	2 oz	60
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
Dinner:		
Meat or fish	3 oz	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter.	1 teaspoon	5

One Thousand Calorie Diet

Protein 75 gm, Fat 42 gm and Carbohydrate 85 gm.

Breakfast.		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Coffee ad libitum, with milk	1 oz	30
Luncheon		
Lean meat, fish	2 oz	60
or		
Cottage cheese	3 oz	90
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner		
Lean meat or fish	3 oz	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit.	1 serving	100
Whole milk	1 glass	200
Tea or coffee		Ad libitum

years ago that individuals on diets as low as 450 calories daily will remain in nitrogen balance so long as the protein is held at 60 gm. Since Newburgh and his associates at the University of Michigan are among the foremost advocates of radical dieting for reduction in obesity, I am offering here in Table 18 their full reduction diets, necessarily altered here by the omission of sample menus

and enhanced by the addition of household measures where they have been omitted. The reader will find food value tables in the article on Diabetes.

Newburgh and his group routinely use the 450 calorie diet. They point out that green leaves and fruits are emphasized in this diet, the bulk thus affording partial compensation for meagerness and also supplying vitamins; however, vitamin B complex is prescribed as a supplement. The skimmed milk supplies nearly 0.5 gm. of calcium which is sufficient for an adult, and practically all of the protein is of animal origin. Fluid intake is not limited.

TABLE 19.—A REDUCING DIET FOR CHILDREN SUPPLYING BETWEEN 1100 AND 1200 CALORIES AND P 75, F 35, AND C 125

Fruits	All cooked and raw fruits except banana, ½ cup or 4 ounces
Fruit juices	Tomato, orange, or grapefruit, 1 cup or 8 ounces
Eggs	Boiled, poached, or scrambled egg without fat, 1
Cheese	Any variety, 2 ounces
Meats	Poultry, lamb, beef, liver, or fish, 3 to 4 ounces
Vegetables	Spinach, lettuce, celery, tomatoes, string beans, cabbage, Brussels sprouts, chard, cauliflower, broccoli, onion, asparagus, ½ cup at each of two meals
Salads	Any of the above vegetables or fruit served with lemon and mineral oil dressing, ½ cup at each of 2 meals
Desserts	Fruit, gelatin, sherbets, skimmed milk puddings, ½ cup at one meal
Breads	Preferably whole wheat or rye, ½ slice at each meal, Ry-krisp
Beverages	Skimmed milk, not over 1 pint daily, cocoa made with skimmed milk, saccharine to be used as sugar; ¼ grain tablet equalling 1 teaspoon sugar

SAMPLE MENU

Breakfast	*Dinner or Lunch*	*Lunch or Dinner*
1 cup orange juice	3 to 4 oz lean meat or fish	Cottage cheese on lettuce, 2 oz
1 egg	½ cup cooked spinach	½ cup asparagus salad
1 glass skimmed milk	½ cup orange and grapefruit	½ cup string beans
½ slice whole-wheat bread	Salad on leaf of lettuce	½ slice bread
	Mineral oil mayonnaise	1 glass skimmed milk
	½ slice bread	½ cup frosted raspberries
	1 glass skimmed milk	
	Lemon sherbet	

Newburgh says that upon a diet of this type the patient will lose from 3 to 5 pounds a week on the average and that he may be assured that he will lose 50 pounds (23 kg.) in three or four months. It is said that after a few weeks when patients are convinced that they are really losing at the promised rate they find it less trying to continue the plan; however, for those who work hard and cannot continue their occupations unless they get more to eat, the diets of higher caloric value are available. Newburgh finds that often such patients can be satisfied with 600 calories and he only allows the 800 or the 1000 calorie diet when absolutely convinced that it is necessary.

However, Bronstein *et al.* (1942) reported their inability to effect appreciable losses of weight in their series of children regardless of the type of treatment used, and they emphasized the fact that in their experience over a long period of time obesity in mentally adequate children tended to correct itself at about puberty, at which time the children become cognizant of their obesity as a handicap and are then willing to cooperate satisfactorily in a dietary regimen. Newburgh stresses the point that the treatment of obesity in children must emphasize behavior rather than diet and that it is an integral part of the treatment to teach them to control their whims and desires and to help them develop a sense of proportion. He says that sharp underfeeding may be too great a load when coupled with the correction of behavior and that if the cal-

allowance below that which is normal, but it is doubtful if this serves any very useful purpose provided the patient is not allowed to gorge herself on water during the periods of greatest weight loss There are physicians, however, who stoutly maintain that water restriction is of great value in that as water is withdrawn from the tissues the other deposited substances are carried with it. The use of diuretics is even sometimes recommended.

Psychotherapy.—Strang's experience accords with that of all who have succeeded in gaining the cooperation of obese individuals sufficiently to obtain results. "One is astonished at the unanimity with which patients reported a return of vigor, a feeling of well-being and resistance to fatigue which had been lost for months or years. A great variety of obscure symptoms and minor ailments disappeared." Headache and difficulty in breathing usually disappear very rapidly, and as a whole the symptomatic improvement exceeds what can be accounted for by the relief from the mechanical burden of only a relatively few pounds Menstrual disturbances often strikingly improve Nicholson (1946), of Duke University Hospital, reported the successful treatment of

patients that he studied were found to have some type of psychoneurosis in

afford them Swimming is very excellent because of the added energy loss incident to the prolonged cooling of the body surface, but it should be noted that the reducing value of any exercise is lessened as soon as skill is acquired Bauman advised the daily walking of two miles in forty-five minutes or less, or calisthenics lasting ten minutes morning and night; he found that ordinary housework does not replace systematic exercise Strang and his associates were skeptical of the value of exercise, maintaining that routine calisthenics do not make up for the increased food intake as a result of the stimulation of appetite

They felt that the individuals who *most need rapid* weight reduction because of impending exhaustion of the circulatory apparatus after years of chronic strain upon it are the very ones in whom the *genuine work necessary* to accomplish a real loss of 300 to 400 calories cannot be permitted Newburgh warned that individuals on a 450 calorie diet may become *acidotic if they* indulge in much exercise, and he pointed out that exercise is usually a much more difficult way of reducing than by limitation of food since, *according to* his calculations, an individual must walk thirty-six miles to rid himself of one pound of adipose tissue.

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dangerous. Though ...

normal limits for their actual size and weight, they were much above normal if computed upon the basis of ideal weight. For instance, a woman, aged forty-one, whose ideal weight was 133 pounds, actually weighed 216 pounds Her basal metabolic rate was minus 4 in relation to her actual weight but plus 23 in relation to her ideal weight. "In other words this patient as far as her real ...

ther whipping up of the rate with thyroid substance should certainly be approached with full caution. Bulger (1936) made the point that in the obese adolescent especially the drug should not be used, since we do not know "to what extent such tinkering may upset neuroendocrine equilibria." Bruch (1941) stated that in order to obtain a stimulating effect on the metabolism much larger doses are needed than are generally given to obese patients and that the claims for the specific value of thyroid substance in the treatment of an obese child can frequently be discarded on the basis of insufficient dosage alone. Newburgh (1942) said that in his opinion only when the occasional patient is encountered whose basal metabolic rate is pathologically *low is* thyroid medication justified. Andersen (1940) reported in detail three cases of ... in which he believed ...

connection with the use of thyroid gland preparations; in eighteen ... the thyroid treatment had been instituted on account of simple obesity.

Benzedrine Sulfate (Amphetamine).—Recent reports of the satisfactory use of this agent are those of Colton *et al.* (1943), Albrecht (1944), Pelner (1945), Kunstadter (1947), and Freed (1947). It is alleged that use of the drug improves discipline and enables the patient to follow his diet with greater ... his appetite is lessened however, it should be noted that benze... *of appetite but rather that* its ... Albrecht felt that in some respects benzedrine is *too effective an adjunct* to the restricted diet, many patients seek its continued use as a "crutch " Colton *et al.* felt that it should be used *only* as a *temporary* expedient to facilitate the formation of restricted eating habits, their best results having been obtained by the administration of

5 mg. (1/12 grain) upon arising, 5 mg. at 11 A.M. and 5 mg at 4 P.M. Freed (1947) found that occasionally a patient requires 10 mg. (1/6 grain) at one or more times during the day, but that after two months or more the effect becomes more or less fixed so that the altered eating habit remains after the drug is discontinued. Not everyone finds the drug useful however; indeed Howard (1947) said he believed it to have no value because its power of diminishing the intake of food is lost after a very few doses.

Freed (1947) felt that there is very little danger of causing addiction with this drug; he listed the following side reactions, none of which he considered of much significance. dryness of the mouth, temporary exhilaration with a sense of intoxication that may last for a few days, insomnia if the agent is taken

nancy

Other Drugs.—Bram (1946) proposed the use of *digitalis* leaves, 1 to 2 grains (60 to 120 mg.) three times daily at meals, to reduce the appetite; this seems to me a drastic step to take for digitalis is a very potent agent. Greene (1940) used the tincture of *belladonna*, alone or with a sedative, in a small series of cases, in quite a large proportion of which the appetite was reduced; this is another potentially toxic agent. *Dinitrophenol* should be used under no circumstances whatsoever for there is ample proof of its highly toxic nature.

Contraindications to Drastic Dieting.—These are felt to be the presence of a tuberculous lesion, myocardial disease and advanced cardiovascular-renal dis-

nant.

DISEASES OF THE GASTRO-INTESTINAL TRACT

STOMATITIS

Herpetic Stomatitis.—The studies in recent years of Black (1938), Dodd *et al.* (1938), Woodburne (1941), and Scott and Steigman (1941) make it imperative now to recognize as a single entity an acute infectious gingivo-stomatitis that is caused by the virus of herpes simplex and embraces the maladies formerly separately recognized as catarrhal, aphthous and ulcerative stomatitis. In the primary attack, most often occurring in infants and young children, the clinical picture is usually characterized by systemic infection with fever and irritability, and by soreness of the mouth, red swollen gums, oral fetor and regional lymphadenopathy. In some cases none, in others a few, and in still others many diffuse small ulcerations may appear anywhere in the mouth. In most instances the constitutional symptoms disappear in a few days but the oral lesions often persist for some days or a week longer. According to this new conception of the disease the well-known "canker sore" of children or adults, which occurs without other involvement in the mouth and without constitutional symptoms, would merely be evidence of recurrent local attacks of this virus in individuals who had already won constitutional resistance through the primary attack.

The primary attacks of herpetic stomatitis tend to occur in family outbreaks and among people who are malnourished, though to be sure no direct relatio [illegible] often accompa [illegible] hat of herpes simplex. This disease occurs most frequently in infants under 6 months of age but it has been found to occur sporadically in adults, and it is thought that perhaps such persons may serve as sources of infection for susceptible infants. Adults have also been found to harbor and spread the virus when they themselves demonstrated no evidence of infection with it.

One should remember that pemphigus, erythema multiforme, dermatitis herpetiformis, lupus erythematosus and lichen planus sometimes appear in the mouth. It is thought that in a few cases electrogalvanism from dissimilar metallic dentures has caused oral ulceration.

Gangrenous Stomatitis (Cancrum Oris; Noma).—This type of stomatitis is very horrible, but fortunately occurs rarely and then almost exclusively in young children who have been debilitated by a severe bout of illness; Adelsberger (1946) described a widespread outbreak in one of the concentration camps of the Germans during War II. A few institutional epidemics have been reported, however, and Eckstein (1940), having gone to Turkey from Germany, to his surprise saw many cases there, there are also evidences in the literature that this malady is seen not infrequently in the Far East. Beginning as a small ulcer on the mucous membrane of the cheek, lip, or gum, a spreading gangrene rapidly destroys a large portion of one side of the face, death nearly always results in from one to five days. The alleged causative role of the Vincent organism in these cases has never been proved;

perhaps some of them are really atypical fulminating agranulocytosis. Eckstein felt that noma is probably a toxic form of severe herpetic (ulcerative) stomatitis.

Parasitic Stomatitis (Thrush).—This malady, which is caused usually by the hyphomycete, *Monilia albicans*, more rarely by a number of other and quite dissimilar fungi, occurs sporadically and sometimes epidemically among nursing infants. It is generally considered to be due to contamination from imperfectly sterilized nursing bottles or nipples, from the introduction of unsterile cleansing solutions into the mouth, and from the mothers' breasts or from the hands of attendants. Premature, weak athreptic infants, or those suffering from other infectious diseases, are especially predisposed to thrush, but it may also attack otherwise healthy infants. The lesions consist of small gray-white or yellow-brown patches, somewhat resembling milk curds, scattered over the cheeks, gums, lips and tongue; their removal, which is difficult, leaves a slightly bleeding area. Examination of one of these crushed "curds" reveals the organism. The attack usually clears up in two or three days, but hospitals fear thrush because an epidemic not infrequently fails to yield even to vigorous treatment, and without treatment may run a course of several weeks. A few cases of generalized cutaneous monilial infection have been reported and very rarely generalized systemic invasion occurs. MacGregor and Henderson (1943) reported two cases of intestinal thrush in young infants, both of whom died, and a few cases of thrush of the kidney and of the bladder have been reported.

Mercurial Stomatitis.—The first symptoms are metallic taste and soreness of the teeth upon chewing, then the gums become spongy, swollen and tender, and they bleed very easily, the breath is quite foul and the salivary glands are swollen and tender. In extreme cases ulceration, loss of teeth, and even necrosis of the bone may take place.

Bismuth Stomatitis.—This type of stomatitis is characterized by a blue-black line along the margin of the gums, soreness of the gums, salivation, and in severe cases ulceration.

THERAPY

Herpetic Stomatitis.—During the attack, the soft foods, such as milk, slightly cooked eggs, soups, custards, and the like, are the only foods that adults can take with any sort of comfort, the feeding of infants sometimes becomes quite a difficult problem. Local treatment consists in the use of mouth washes such as the following: tincture of myrrh, 1 part to 25 or 50 parts of water; potassium permanganate, 1 part to 8000 parts of water, or some such mixture as the following, which is a very satisfactory mouth wash:

℞	Thymol (saturated solution)	℥ij	64.0
	Hydrogen peroxide	℥ij	64.0
	Glycerin	℥ij	64.0
	Potassium chlorate (saturated solution) to make	℥viij	250.0
	Label. Dilute and use as mouth wash		

In infants, who cannot of course gargle or rinse the mouth, it is necessary to apply these washes on a cotton swab. The saturated solution of boric acid has long enjoyed a reputation as the ideal mild mouth wash, a reputation entirely undeserved for the reason that it is practically worthless as an antiseptic.

In recurrent "canker sores" the silver nitrate stick is very effective. It

should be firmly applied to the bottom and sides of each of the ulcers, rinsing the mouth with water afterward if the caustic and metallic taste is very objectionable In more diffusely ulcerated cases the use of potassium chlorate to be swallowed is recommended by several physicians of wide experience, despite the well-known ability of this drug to cause methemoglobin production; it is excreted partially through the salivary glands and thus the ulcerated surfaces in the mouth are continuously bathed in a potassium chlorate solution Bradbury stated that the drug is almost a specific when used internally, recommending for an adult 10 grains (0.65 gm.) three times a day, to be taken well diluted, and for a child of six years, 3 grains (0.2 gm.) every four hours. Wise and Parkhurst recommended 20 grains (1.3 gm.) three times daily for the adult.

In recurrent cases, Woodburne (1941) successfully employed the repeated *vaccination method of treatment: smallpox vaccination is performed at intervals* of one to two weeks unless a "take" occurs in which case the reaction is allowed to subside before vaccination is again performed; in Woodburne's series vaccination was performed twice in three cases, three times in two, four times in five, five times in four, six times in two, seven times in two, eight times in three, fifteen times in one. Grace (1943) also reported greater improvement in two recurrent cases, in one of which vaccination was performed twelve times and in the other six times.

Gangrenous Stomatitis.—Very rarely early and radical excision of the gan-

eight died, but of twenty-one treated by local injections of "antigangrene serum" into the healthy surrounding tissue, eleven progressed to complete

ful in these cases. Adelsberger (1946) said that the combined use of sulfonamides and nicotinic acid was very effective in an outbreak in a concentration camp in which she was confined during War II Vaizey (1946) reported three cases of noma successfully treated with penicillin in Addis Ababa.

Parasitic Stomatitis (Thrush).—Until recently, perhaps the most effective

swab every two hours during the day and the entire mouth was swabbed

Herpetic Stomatitis, above) as a routine practice throughout the period in

Poisoning).

Bismuth Stomatitis.—See under Syphilis.

DYSPEPSIA

(Indigestion)

It is mandatory upon the physician to approach the diagnosis and treatment of every case of dyspepsia by the purely eliminative process, for though it is undeniably true that the majority of digestive complaints are due to either sensory, secretory, or motor disturbances, and are therefore functional rather

that the patient has been shown not to have gastritis, peptic ulcer, or cancer, the functional disturbances remain to be considered—provided that two further possibilities are also eliminated, namely, dyspepsia due to dietary indiscretion, and secondary, so-called "reflex" dyspepsia. *Dietary indiscretion* is usually encountered in those of a fulsome habit, who have regard neither for the quantity nor the quality of their food and drink, and who disdain all the decencies of table deportment; occasionally, however, an individual suffering from this type of indigestion will not be one of the gobblers but merely a person who suffers from the taking of small and even well-masticated quantities of certain foods, such as fried and greasy dishes, heavy hot breads, excessively hot or cold dishes, etc. Any of the symptoms of indigestion may be manifested, and they will all usually disappear if the offending articles are withheld from the diet, or if the individual is made to curb his gluttony—that is to say, if a silk purse is made out of a sow's ear. *Reflex dyspepsia* may indicate

give rise to gastro-intestinal symptoms of either an acute or chronic nature, and that a functional dyspepsia is often associated with disease of the genito-urinary organs, hyperthyroidism, the anemias and pulmonary tuberculosis.

NERVOUS INDIGESTION

This type of dyspepsia, whose sufferers are legion, is characterized by the following facts the gastro-intestinal syndrome changes frequently, so that at one time the picture will be dominated by a symptom of one sort and at another time by a symptom of another sort altogether, there are usually other psychasthenic complaints, such as palpitation, poor circulation, fatigue, pe-

culiar forms of headache, and the like; there is no definite relationship between the quantity or quality of food taken and the type and degree of the gastro-intestinal disturbances; and the symptoms are very dependent upon the state of mind of the individual at the time he partakes of a given meal. The most usual complaints are of fulness and discomfort in the epigastrium, pain, eructation of gas, nausea, vomiting and difficulty in swallowing. Often the appetite is poor, but sometimes a patient, believing that only by forcing himself to eat will he get well, is given to inordinate performances at table. Others attempt to treat themselves by eliminating articles one after another from the diet in the hope of finding the offending food, such individuals not infrequently maintain themselves in a condition of semistarvation, and affect their malady not in the least unless it be to make it worse. According to Halsted *et al.* (1946), soldiers complaining of nervous indigestion constituted a major medical problem during War II. In a study of 110 soldiers with such complaints under combat conditions they found a psychoneurosis in 84.5 per cent of the group.

Psychotherapy.—In Alvarez' (1943) excellent treatise on this subject he says that very important points in the psychotherapy of nervous indigestion are the taking of a thorough history and the making of complete and careful physical, roentgenologic and laboratory examinations; many patients lose interest in their symptoms if the result of all this reveals no evidence of serious disease. He says that often the physician can be of great help to certain patients only by teaching them to acquiesce to conditions in their lives against which it is futile to struggle. Some, too, must be shown the necessity for rest and how to achieve it; others, how to avoid getting all stirred up over little things and reviewing at great length painful or annoying experiences that more sensible people would promptly forget. Alvarez feels it important to obtain sufficient sleep for sufferers from nervous indigestion and that the use of barbiturates is fully justified in patients who cannot relax sufficiently to sleep unaided.

Physical Therapy.—I think it is common experience that only a certain sort of individual is helped by massage and that sort of thing, but Alvarez probably finds many observers in agreement with him when he says that physical therapeutic measures are invaluable in selected cases because they keep the patient busy and hopeful and bring him back repeatedly under the influence and guidance of the physical therapist and the physician These measures, he says, keep the patient out of mischief and out of the hands of the quacks, but it seems to me that one must be very careful not to stray over into that territory oneself.

Smooth Diet.—Alvarez believes the virtue of the smooth diet to lie not in the fact that cellulose is so indigestible and by its presence likely to interfere with the action of digestive ferments on starches and other foods, but rather in the assumed existence in the sick individual of areas of reversed peristalsis [illegible] is I do not

celery, tomatoes, cucumbers and pineapple, many of the green [illegible] raisins, berries, jams full of seeds, nuts and many of the raw fruits Beans, cabbage, onions, green or red peppers, melons, cucumbers and peanuts he considers notoriously "gassy." Browne *et al.* (1947) said that since the extremely irritable gastro-intestinal tract is stimulated by any and all foods,

some patients may be benefited by a twenty-four hour starvation period, and that in all cases the instruction to grind meats and purée fruits and

dishes are really only employed by restaurateurs to persuade one to be indiscreet in diet.

PYLOROSPASM

Pylorospasm, unassociated with ulcer or other organic lesion, is a spasmodic constriction of the pylorus occurring usually at the height of digestion. There is pain, which may be very intense, eructations and vomiting, sometimes with-

no food and of course wastes away rapidly

THERAPY

known ability to relax involuntary muscle Infants are relatively insensitive to it, in pylorospasm, doses of 1/75 to 1/25 grain (0 8–2 4 mg.) are sometimes used in them with good effect and no significant side actions, though it is certainly advisable to make preliminary trial of smaller dosage.

Mackay (1941) reported the cure of the condition in thirty-one, and its inprovement in four or more, of forty infants given atropine methyl nitrate (eumydrin, a British proprietary available in this country as harvatrate); dosage· 0 5 to 1 0 cc of 1:10,000 solution by mouth, twenty to thirty minutes before the six daily feedings per twenty-four hours, increasing 0 5 cc up to 2 0 to 3 0 cc. per dose, even further increases being made if vomiting was not checked Apparently the use of eumydrin has gone very far in England, for Smallpeice (1946) felt obliged to protest its use before diagnosis since she seemed to feel that some infants were thus being prevented from obtaining surgical aid in time to save their lives

Dry Diet.—Use of a diet that would be difficult to vomit was advocated by Sauer some years ago The following case report of Speidel is of great interest:

"Z C, female, aged twenty-one, came to my office on September 28, 1925, complaining of general abdominal distress, loss of weight, constipation, poor appetite and vomiting. The onset

food. She was given water half way between meals in whatever quantity she desired. Improvement began at once. On December 11th, the atropine was administered by mouth instead of hypodermically and the dry diet was continued"

Eleven years after this patient first came under observation, Speidel (1936) reported her as still having to adhere rigidly to the dry diet and atropine. But

dilatation of the vesical sphincter had been resorted to.

In Infants.—In pyloric stenosis in infants it is usually held that immediate operation is indicated, but Sauer has advised the trial of thick cereal feedings for a time; if the vomiting fails to subside in a week or two and the child does not increase in weight and general condition, operation must be resorted to, and of course it is advised at once when infants are first seen in a very emaciated unresponsive state. The operative mortality in the 550 cases surgically treated by Ladd *et al.* (1946) in the preceding ten years was 0.9 per cent, though in the last 225 patients operated upon there had been no fatality at all. In connection with the dry diet it is of interest to note that in Mackay's (1941) series of patients successfully treated with eumydrin (see above) the only ones not responding were those who had a high fluid intake. Sauer's mixture (according to a communication from him in late 1946) is skimmed milk, 9 ounces, water, 12 ounces, farina or rice flour, 4 tablespoonfuls; dextrimaltose, 3 tablespoonfuls; boil an hour in a covered double boiler. From 3 to 5 tablespoonfuls of this is given six to seven times daily, scraped off a narrow tongue depressor well back in the mouth. Fluid is supplied as 6 per cent dextrose in Ringer's solution by rectum. Sauer (1946) said that this dietary method of treatment in infantile pyloric stenosis is successful in at least 50 per cent of cases.

Lavage.—In an aged patient in a very poor physical condition Scriver (1931) resorted to the use of the tube and thorough washing out of the stomach twice daily, the patient was saved and became able to retain a diet upon which he gained weight. Subsequent x-ray examination showed disappearance of the previously observed atony. Mackay (1941) obtained no benefit from routine lavage in her series of infants.

HYPERCHLORHYDRIA

This condition, which is more frequent in young and middle-aged persons than in older individuals, is the most common of all gastric disturbances. The symptoms are caused by a more than normal production of acid (*not* an increase in the relative acidity of the juice) during the digestion of a meal, but it should be borne in mind that a gastric analysis revealing an apparently normal acidity does not necessarily rule out hyperchlorhydria for the reason that the "normal" acidity of the stomach contents during digestion varies widely and an individual may actually suffer from the symp-

and extend into the back and up into the throat. There is heartburn and eructation of acid fluid; occasionally there is also vomiting of very acid stomach contents that burn the throat and mouth. Light and starchy repasts are

more prone to produce an attack than are heavier meaty meals The patients are often otherwise in good health, have a good appetite and are in good flesh

THERAPY

The usual remedy for an attack of this kind is to administer sodium bicarbonate in a dose of 15 grains (1 gm.) when the pain appears and repeat several times if necessary The large doses often taken by the layman are not necessary and may even induce the production of more acid; and it should be pointed out that the drug is to be taken in warm, but not very hot, water, for the latter converts bicarbonate into carbonate that may in itself be irritating. The reader is urged to turn to the discussion of the various antacids as used in the treatment of peptic ulcer, for what is there said applies equally here.

HYPOCHLORHYDRIA (ACHYLIA GASTRICA)

Rafsky and Weingarten (1947) confirmed the fact that there is a tendency to a diminished acidity in the normal aged, but in only 17 per cent of their series of forty-seven individuals was a true achlorhydria found The symptoms of hypochlorhydria are usually few because gastric digestion in these cases is vicariously performed by the intestine. However, there is sometimes loss of appetite and a sense of fulness after eating Nausea and vomiting are rare. In a few cases there is severe pain, heartburn and eructations just as in hyperacidity, sometimes, too, periods of diarrhea and constipation alternate. Schindler (1940), with his flexible gastroscope, has found some type of gastritis in surprisingly many patients with hypochlorhydria

THERAPY

Hydrochloric Acid.—For many years it has been assumed that hydrochloric acid may be expected to act in the following ways in cases of hypochlorhydria: (a) as a stomachic, (b) to form acid albuminates and so aid in proteolysis, (c) to release pepsin from the pepsinogen of the glands, (d) to promote an acid medium for the action of pepsin, (e) as an antiseptic, (f) to stimulate pancreatic secretion and possibly gallbladder emptying, (g) to improve tonus and peristalsis, especially that concerned in gastric evacuation, (h) to aid in the

It seems advisable to continue a description here of the method devised by Dodson a number of years ago

(a) The U S P dilute hydrochloric acid should be given in as large amounts as the patient will tolerate—as much as $2\frac{1}{2}$ drachms (10 cc.) during the digestive period if possible.

(b) Instead of employing the continuous sipping method, it is preferable to have acid taken in fractional doses of 30 minims (2 cc) at a time; one such dose in the middle of the meal and the same amount at fifteen-minute intervals thereafter for an hour or more, lengthening the intervals rather than decreasing the number of doses if unpleasant symptoms arise.

(c) Two ounces (60 cc) of water, grape juice, lemonade, or any other non-

food. She was given water half way between meals in whatever quantity she desired. Improvement began at once. On December 11th, the atropine was administered by mouth instead of hypodermically and the dry diet was continued."

Eleven years after this patient first came under observation, Speidel (1936) reported her as still having to adhere rigidly to the dry diet and atropine. But she was otherwise an apparently healthy young woman and had given birth to a normal baby. Interestingly, after delivery she became unable to empty the bladder and obtained permanent relief of this spasm only after mechanical dilatation of the vesical sphincter had been resorted to.

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events is quite characteristic. Pain comes on an hour or more after [illegible] *it is usually of the mild pressure type* but may be very severe and boring and extend into the back and up into the throat. There is heartburn and eructation of acid fluid; occasionally there is also vomiting of very acid stomach contents that burn the throat and mouth. Light and starchy repasts are

more prone to produce an attack than are heavier meaty meals. The patients are often otherwise in good health, have a good appetite and are in good flesh

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thereafter for an hour or more, lengthening the intervals rather than decreasing the number of doses if unpleasant symptoms arise.

(c) Two ounces (60 cc) of water, grape juice, lemonade, or any other non-

alkaline vehicle may be used as diluent for each dose, but the ingestion of other fluids during the meal should be restricted

(d) It may be well to attempt the stimulation of normal acid production by having one meal daily consist almost entirely of carbohydrate, accompanied by the taking of acid as usual Tests should be performed periodically throughout the treatment to determine whether the secretory mechanism has been reactivated to any degree.

It is well to have the acid taken through a glass tube in order to avoid possible injury to the teeth. Hubbard (1931) found it worth while to use also an alkali-forming diet in patients who show evidences of systemic acid-base imbalance upon prolonged administration of hydrochloric acid. The addition of citrus fruits and green vegetables to the diet will considerably reduce the excessive acidity of the urine.

Lemon Juice.—Bethea and Claunch (1939) reported that 30 cc of lemon [illegible]

the alkali reserve after absorption

Glutamic Acid Hydrochloride.—In combination with hydrochloric acid, glutamic acid forms a white powder which, in contact with water, quickly yields hydrochloric acid. The drug may be given in capsules of 5 grains (0.3 gm) with water. Shay and Gershon-Cohen (1936) obtained satisfactory clinical results by [illegible] after the beginning of the meal an[illegible] of the capsule[illegible] *this drug satisfactory.*

Digestive Ferments.—In Dobson's studies, the use of the essence of pepsin and the extract of the gastric mucosa, gastron (the dose of either of which is [illegible] absence of acid [illegible]

submitted to the members of the American Gastro-Enterological Association "From this report it is seen that among the members of the American Gastro-Enterological Association many do not prescribe digestive enzymes at all, while those who do employ such enzymes confine their use almost wholly to cases of demonstrated or believed enzyme deficiency It is further noticeable that almost all who prescribe them show no great enthusiasm over the results of their use, except possibly in the case of pancreatin in proved pancreatic deficiency. The conclusion is therefore inevitable that they are of minor importance in therapeutics "

ATONY

Atony is characterized by a loss of muscular tone, so that the stomach fails to empty itself in the usual time and finally becomes more or less *chronically* dilated The victims of this condition are usually nervous individuals who habitually eat inordinate amounts of difficultly digestible foods and drink large quantities of fluids—until the gastric upset occurs, *after which they often* attempt to subsist on little more than starvation rations. The most common subjective symptom is a feeling of fulness that appears long before hunger has been satisfied, *nausea, eructations, headache, and dizziness* also frequently

occur, but actual pain and vomiting are rare A characteristic symptom is that food is tasted long after it is eaten Gastric analysis shows food remnants seven hours or more after a meal, and on roentgenographic examination the stomach is found to be dilated and its peristaltic action impaired.

THERAPY

Read the treatment of nervous indigestion at the beginning of this chapter; indeed, there is little more to do for these patients than attempt to apply that treatment The diet should be restricted to easily digestible foods to be taken in small amou
hyperacidity o
as outlined in
long recommended, has never been shown to have any value.

INTESTINAL FERMENTATION

The patient troubled with intestinal fermentative dyspepsia complains of distention with gas, abdominal discomfort and pain, and the daily passage of several liquid *or semisolid stools* accompanied by much *gas* The *stools are* quite acid and show evidence of a marked impairment of starch digestion but usually a quite normal digestion of fats and proteins. However, Tuft and Tumen's (1946) study of their cases led them to conclude that sugar *and* fat intolerance may be a more frequent cause of these symptoms than is usually suspected, at times there is also an over-abundance of fermentative organisms present. The patients are usually otherwise in good health, except for the stigmata of neurasthenia, and are not infrequently asymptomatic for long periods

THERAPY

Dietetics.—Occasionally these patients are able to identify the particular

under the conditions is one rich in protein and poor in carbohydrate, with

spices and sweet milk. Meat, eggs, fish and cheese, the latter preferably, are allowed Green vegetables must be cooked and puréed. Cooked fruit, fruit juices, nuts except peanuts, are allowed Of course the ultimate aim of treatment is to allow gradually increasing quantities of the prohibited foods until a relatively normal dietary can be resumed.

Lactic Acid.—Althausen (1935), who especially advised the use of buttermilk, often found it necessary to build up tolerance by beginning with small amounts and working up to a quart a day. He also used lactose at mealtimes, beginning with a teaspoonful and increasing to a tablespoonful

Kaolin and Charcoal.—These substances are sometimes used to adsorb gases, bacteria and toxins, and to coat the intestinal mucosa.

Intestinal Antiseptics.—The drugs which were formerly called "intestinal antiseptics," salol, betanaphthol, zinc phenosulfonate (zinc sulfocarbonate), and so on, never had any value here, nor it is likely that calomel, so freely

taken by individuals suffering from this complaint, is of any worth either. I have not seen the report of any study of the use of sulfasuxidine or sulfathalidine in these cases, but think it quite unlikely that they would bring relief to these patients.

Carminatives.—The carminative drugs are said to promote the expulsion of gas without in themselves acting as cathartics. This group of drugs comprises alcohol, capsicum, cardamom, cloves, ginger, mustard and the volatile oils generally. A very satisfactory carminative prescription is the following:

℞	Tincture of capsicum	ʒss	2 0
	Spirits of peppermint	ʒij	8 0
	Tincture of ginger	℥ij	60 0
	Alcohol to make	℥iv	120 0

Label: 1 teaspoonful well diluted every half hour until relieved.

I have heard it said that persons who suffer the sort of gaseous distention that wakes them in the night are often quickly relieved by the taking of bile salts, such as decholin, in doses of 4 to 8 grains (0.25–0.5 gm.). I do not know how such relief is brought about; but if it is, it is, I suppose.

GASTRITIS

Acute gastritis is a not infrequent accompaniment of the acute infectious diseases and is one of the outstanding symptoms of poisoning with such substances as the metals, alcohol, acids, alkalis. For the management of this condition reference must be had to these subjects as they are discussed elsewhere in the book; chronic gastritis, however, requires to be separately considered.

Chronic gastritis is caused by persistent overeating, by the prolonged ingestion of foods that are digested only with great difficulty, or are taken too hot or too cold, or by the habitual gobbling of all meals; or by the excessive indulgence in tobacco or alcohol, especially the latter; or by the prolonged taking of such drugs as the iodides, copaiba or salicylates. It also occurs as a symptom of ulcer and carcinoma, and may be associated with such diseases as leukemia, pernicious anemia, nephritis, tuberculosis and other constitutional diseases. It is also nowadays assumed that gastritis underlies hyperchlorhydria and hypochlorhydria, so that these conditions may ultimately lose their clinical identities through being merged in the gastritis syndrome. Heart, kidney and liver affections cause passive congestion of the stomach mucosa and ultimately chronic gastritis. Pathologists who have investigated the matter have felt that, whatever the cause of the condition, there occurs a gradual destruction of the glandular apparatus, though this may be preceded by a period of hyperactivity. However, one must bear in mind that such studies will always be embarrassed by the fact that the normal histologic appearance of the gastric mucosa is none too well known. A very promising approach to the subject is that being made by Schindler and his associates who, as a result of their observations with the flexible gastroscope, are classifying cases into superficial, atrophic and hypertrophic types.

The symptoms are variegated and are such as may occur in any of the dyspepsias. Diagnosis is often difficult, but early morning vomiting of mucus and the finding of large quantities of gastric mucus in the stomach after a test

meal, or after a short period of fasting, are very suggestive symptoms, as are also the findings with the gastroscope referred to above.

THERAPY

Diet.—Dietary treatment is essential in these cases. Of course the offending food or drink, if it can be identified, must be absolutely eliminated, and then

used and washing persisted in until the fluid comes away absolutely clear; at the end a pint of distilled water should be run in and out. Depending upon the severity of the case, lavage should be practiced morning and evening, or only in the morning, or only two or three times a week. In Hurst's (1934) experience the use of an ounce (30 cc.) of hydrogen peroxide to the pint (500 cc.) of water effectively removed mucus and was sometimes followed by the appearance of free acid in the stomach.

Vitamins, Liver, Ventriculin, Iron.—Eusterman (1939) stressed the point that one must be sure to provide an adequate intake of vitamins, especially A, the B complex, and C, but Shapiro *et al* (1944) failed to produce any significant changes in the gastric mucosa of five patients treated with a large array of vitamins. Schiff and Goodman (1940) induced marked symptomatic im-

ventriculin, did not indicate that such replacement therapy might be expected to be specifically curative in all cases of atrophic gastritis. Annis (1944),

Acids and Alkalis.—When indicated these agents are used as in hypo- and hyperacidity respectively

PEPTIC ULCER

(Gastric and Duodenal Ulcer)

Gastric ulcer occurs nearly always at a distance of two inches or more from the pylorus, duodenal ulcer is usually located one-half inch or more away from the landmarks separating the stomach and duodenum; pyloric and primary jejunal ulcers are rare It is thought that multiple ulceration occurs in between 20 and 30 per cent of cases. Gastric and duodenal ulcers are sufficiently alike in their symptoms and treatment that they may be

to do so as in peptic ulcer. It is easy to agree with Miller that in these patients it is of the utmost importance that they see the physician deeply interested in their case and that a definite regimen of treatment is instituted confidently and at once. One cannot lightly dismiss the fact that Gill (1947) obtained excellent responses without any dietary restrictions whatsoever in a consecutive series of twenty patients with chronic gastric ulcer who were given a daily hypodermic injection of 1 cc. of distilled water.

Vagotomy

Acting on the concept that the hypersecretion of gastric juice in peptic ulcer is largely neurogenic, Dragstedt several years ago began performing an operation designed to remove permanently and as completely as possible the vagus innervation of the stomach The operation in essence consists in cutting the cardia away from the diaphragmatic hiatus, pulling down the esophagus, cutting the vagi, and then after the esophagus has been allowed to slip up into place again sewing the edges of the hiatus close to the cardia once more Several rather extensive series of these vagotomies for the treatment of peptic ulcer have been reported, the most notable perhaps being those of Thornton, Storer and Dragstedt (1946), Moore *et al.* (1947), and Smith *et al.* (1947). At the time of writing, in the middle of the summer of 1947, perhaps some 350 to 400 such operations have been reported and in almost all the cases the results have certainly been encouraging. Usually the pain and discomfort cease promptly and the ulcer apparently heals The good results are not altogether easy to understand because in many cases gastric acidity is not altered or at least not completely done away with, or if it is greatly diminished for a time it soon returns to normal or above. Experiments have been performed to show that after this operation it is possible, through inflating a balloon in the esophagus or stomach or duodenum, to produce pain, obliging one to conclude that the sensory pathways have not been interrupted; indeed, after the operation hunger and nausea are still experi- [illegible] function normally. It seems that the [illegible] is alteration of gastric motility, the [illegible] either abolished or markedly slowed and decreased in amplitude and caused to become less rhythmical The alteration in motility is usually accompanied by dilatation of the stomach and gastric retention of varying degree. Smith *et al* (1947) have felt that the most likely explanation for the immediate relief of pain and subsequent healing of the ulcer is this striking alteration of gastric motility. However, it is not at all unlikely that a large part of the effect is the result of interruption of the pathways carrying to the digestive tract harmful influences arising in the brain There is indeed one recorded observation of such an effect, that of Wolf and Andrus (1947), who were able to observe in a patient with a gastric fistula and a double vagotomy that reference to topics that induced feelings of anger and resentment in the patient, and that had been associated prior to vagotomy with gastric hyperemia, engorgement and hypermotility, caused after vagotomy no observable changes in gastric function though the patient manifested all the other evidences of anger and resentment

This development of vagotomy in the treatment of peptic ulcer is certainly one of the most interesting advances that has been made in many years, but it is still far too soon for anyone to be able to say authoritatively to what

extent the procedure is applicable to the average sort of case as seen in everyday practice. Many more operations have to be performed by many more men before we can be certain of the indications, the contraindications and the clinical side effects of this procedure, whether it evokes physiologic changes of some nature not yet observed, and how long the effects may last. At present we do know that the alteration in motility usually causes the stomach to retain food for a very long time after the operation, that the patient is oftentimes made very uncomfortable by this (Machella's, 1947, restoration of gastric motility in two patients through the administration of the urethane of β-methylcholine chloride is very interesting), and that he is sometimes troubled with diarrhea for quite awhile after the operation More time must also be allowed to pass in order to determine the operative mortality in the hands of the general surgeon.

Medical versus the Older Type of Surgical Treatment

The old controversy of medical versus surgical treatment (other than vagotomy) has been so thoroughly resolved that Lahey, himself a surgeon, was able to say in 1943: "No one today, I think, can defend primary surgery in the treatment of ulcer All of our ulcer patients come to us only as medical failures." Internists would not like the term "medical failures," but I think would prefer to say, with justification, that the indications for operation arise essentially from the complications of ulcer. Palmer (1942), who has had vast experience with ulcer, has said that the most frequent indication for operative treatment is cicatricial obstruction (i e, stenosis), but that even it does not necessarily require operation unless the stenotic lumen is reduced to a diameter of only 3 mm or less as judged by fluoroscopic study

should be operated upon Of course acute perforation is recognized by practically all observers as a most urgent indication for operation but Palmer says that subacute and chronic perforations do not necessarily constitute indications In selected cases of massive hemorrhage he believes that surgical attempts to tie off the bleeding artery or even to excise the lesion may properly be elected, and that in certain instances of recurring massive hemorrhage

medical treatment One might interpolate here that roentgenologists admit their inability to determine whether the lesion is malignant or not in 10 per cent or more of gastric ulcers, and that Walters (1942) said that the clinical symptoms thought to be pathognomonic of benign gastric and duodenal ulcer occurred in a third of the cases of carcinoma in which operation was performed at the Mayo Clinic, temporary effective response to a medical regimen having occurred in 80 per cent of this group, Walters therefore felt that most gastric ulcers should be removed surgically without too much delay, but here again Hinton (1946) disagrees, pointing out that the mortality from routine subtotal resection for gastric ulcer far exceeds the possibility of malignant degeneration in nonoperated cases Palmer thought that jejunal ulcer may be treated medically, although as a rule its management is more

the small incidence of patients who had been treated for ulcer among their 1260 cases of kidney and ureteral stone was not of statistical significance, while Eisele (1940) found the incidence rather high among his 505 cases.

Substitutes for the Sippy Alkalis.—The neutral antacids, tricalcium phosphate and trimagnesium phosphate, have been tried, usually together in doses of 10 to 25 grains (0.6–1.5 gm.) each. They do not often adequately serve to neutralize the amount of acid present. Mutch, in England, introduced synthetic hydrated magnesium trisilicate, which has since been satisfactorily used *in a dosage of 15 to 30 grains (1 to 2 gm.)*, occasionally as high as 60 grains (4 gm.), by a few n [illegible]
advantage claimed [illegible]
losis. Heffner *et al.* [illegible]
but no evidence of toxicity therefrom.

Kirsner and Palmer (1941) compared antacids in peptic ulcer patients with a technic comprising hourly removal of gastric contents for determination of relative acidity and hourly administration of the alkali. The drugs studied were calcium carbonate, sodium bicarbonate, aluminum hydroxide, tri-calsate, tribasic calcium phosphate, magnesium trisilicate, magnesium carbonate and tribasic magnesium phosphate. Calcium carbonate, in dosage of 2 to 4 gm., and magnesium carbonate, in dosage of 2 gm., were found to be the most effective neutralizers of gastric acidity.

Steigmann and Fantus (1940) found that a number of "antacids" give [illegible]

shared this viewpoint at least with regard to duodenal ulcer for they found that the reduction of intraduodenal acidity is neither great nor long-lasting and may be followed by a rebound increase. Several observers have recently re- [illegible] ulcer has been almost [illegible]

sent to them by their physicans because they were classified as having "intractable" ulcers and that twenty-six of the thirty-four individuals in the group had their symptoms controlled by sodium alkyl sulfate and were so well restored physically that they were accepted by either the Armed Forces or industry. The dosage employed was 3 grains (0.2 gm.) every two hours throughout the day. Unfortunately, however, neither Steigmann and Marks (1944), nor Kirsner and Wolff (1944), were able to duplicate these results.

Atropine.—*Kirsner* and Palmer (1940) reported that atropine sulfate, given orally in four 1/60-grain (1 mg) doses daily, did not affect the reaction of the gastric contents though it did apparently reduce the volume of the secretion. They found it very helpful when used as above in addition to alkali therapy, the result in their opinion being due to atropine's prolongation of gastric [illegible] as well as its reduction of the volume of gastric secretion. How- [illegible]
igh and must cause [illegible]
ally be of any value in view of the notorious resistance of the gastro-intestinal tract to the action of atropine. Despite the fact that most gastro-enterologists say that patients

feel better when they are given atropine, I certainly agree with Gold that it would be well to have this matter put to the test by substitution of a placebo.

Ambulatory with Frequent Feedings (Alvarez Type of Treatment)

While admitting that the Sippy treatment is often effective, Alvarez has the following objections to make: (a) it requires more training, enthusiasm and faith in this particular type of treatment than can be expected from the average busy practitioner, (b) it requires an expensive month in hospital, (c) only a very few patients can be expected to come back to the hospital for subsequent Sippy treatments for each recurrence, (d) the lack of evidence that the period of relief after a Sippy cure is longer than after little or no treatment, (e) the observation that frequent feeding is perhaps the most valuable item in the cure, (f) and the fact that, "whether the profession likes it or not," most patients with ulcer will continue to try to worry through their attacks and keep at their work. In view of these considerations, Alvarez cham-

is that foods which contain scratchy material, such as raw fruit, bran, many of the green vegetables unless puréed, celery, salads, nuts, gristle and berries, are to be excluded Alvarez is not certain that such care is important, but since many patients experience no great privation with this amount of restriction, he feels that "smooth" dieting should be instituted in most cases. Meat is not forbidden Windwer and Matzner (1939) in fact proposed that in addition to the use of lean boiled meat, chicken, cottage cheese and milk,

proteins. (c) The ample supply of amino acids will restore a deficiency believed by some to be a causative factor in the production of ulcer

The important part of the treatment consists in the taking of food between meals The mixture used consists of a quart of milk, two eggs and from 1 gill to ½ pint of cream Of this a glassful is drunk at 10 A.M and another at 2, 4, 8 and 10 P M, with an additional one during the night when awake The

patients with 1 to 4 ounces (30 to 120 cc.) of a mixture of equal parts of milk

Alkalis.—Not routinely used in this type of treatment

Exercise.—The patient is to rest as much as possible on Saturdays and Sundays Walking is about the only exercise that is allowable at any time, golf, gardening and any bodily movements that are likely to cause pulling on

the duodenum are to be given up. Alvarez says: "One must remember that the first portion of the duodenum serves as a sort of hook from which the stomach swings like a hammock, and I believe that this anatomic arrangement has something to do with the tendency toward ulceration at that point. Men often say that it is the hard work in spring or fall, plowing or pitching hay, which brings their recurrences, and I have seen a number of cases in which, even after operation, the patient could stay well only by avoiding lifting and bending. In fact many persons can obtain permanent relief only by changing to a sedentary occupation."

Duration of Treatment.—Most patients are quickly made comfortable on

once or twice in the afternoon, and perhaps again before retiring. Alvarez (1944) said that the patient with ulcer is most in danger of a flare-up or a catastrophe during the hours immediately following a distressing emotional storm, and he therefore suggested that when a patient goes through such a crisis he should not wait for the expected flare-up or hemorrhage or perforation but should immediately start taking food every hour or two; the extra feedings probably most needed are those between the hours of 10 P.M. and 3 A.M.

Aluminum Hydroxide and Aluminum Phosphate

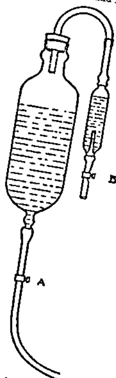
hydroxide in this type of treatment.

The method of treating peptic ulcer with aluminum gels resembles the classical Sippy method in that very ill patients are kept in bed on frequent *feedings of a bland diet; it resembles the Alvarez method in that less severely* ill patients are maintained in an ambulatory state with quite similar frequent feedings. But it differs from these methods of treatment in that it substitutes *for the alkalis of the Sippy regimen, and the lack of alkalis of the Alvarez*

like mass. Unlike the carbonates, they ... es of carbon dioxide and they are not laxative like the magnesium salts; indeed *they are even constipating* though the phosphate gel is found the less offender of the two in this regard. Furthermore they do not induce compensatory acid

Drip Administration.—This method requires hospitalization but it is the preferred method to accomplish rapid healing and also the necessary method in very ill patients The colloidal aluminum preparations are continuously instilled into the stomach through a nasogastric tube at the rate of 15 drops per minute, day and night, for ten days in average cases. The earlier troubles from clogging of an ordinary Levin tube and complaints when a larger Levin tube

FLASK FOR DRIPPING COLLOIDAL ALUMINUM SUSPENSIONS
(After Woldman and Rowland)



Technic.—1 Fill the Kelly (larger) flask to the top with a 1 per cent suspension of colloidal aluminum hydroxide or phosphate while clamp (*A*) is closed 2 Fill the inverted Murphy drip tube with water while clamp (*B*) is closed 3 Insert the rubber stopper securely into the mouth of the Kelly flask and connect the inverted Murphy drip tube to the short rubber tube with screw clip as indicated in the diagram 4 Attach Kelly flask to a hook or standard 2 to 3 feet above the level of the patient's stomach 5 Open clamp (*A*) wide 6 Open clamp (*B*) just enough to allow air to bubble slowly through the water in the Murphy drip tube (about fifteen bubbles a minute) 7. After the rate of flow is established and the nasogastric tube is comfortably in position, attach the outflow tube to the nasogastric tube by a glass connection

was used have now been overcome by the substitution of a soft collapsible hin rubber tube about ¼ inch in diameter. This tube is passed through the ose into the stomach with the aid of a silkworm-gut suture which acts as bturator and is left in place within the tube to prevent its kinking. The tube passed only as far as the end of the esophagus. The older three-flask method delivering the solution has now been replaced by the one-flask method of oldman and Rowland (1941) depicted and described herewith

Since the astringent action of aluminum hydroxide tends to cause constipation, mineral oil is usually given daily, or an enema every other day. Collins (1945) prevents constipation by adding equal parts of heavy magnesium oxide and calcium carbonate to the evening doses of aluminum hydroxide gel Laxative measures may be unnecessary if the phosphate is used.

Oral Administration.—Collins (1945) [illegible]

[illegible]

minations of gastric acidity and the severity of the symptoms, but is never less than 2 drachms (8 cc) and the bedtime dose is never less than 1 ounce (30 cc). If a patient has severe night pain associated with continuous night secretion the bedtime dose is repeated at midnight and at 3 A.M. during the first week's treatment. Amphogel is usually given in the dosage stated by Collins stirred up in a half glass of water or milk; tablets equivalent to 8 cc of the liquid and soluble in water or to be dissolved in the mouth before swallowing, are also used.

Ambulatory Routine.—Collins (1945) says that patients with uncomplicated ulcer and minor symptoms are allowed to continue working and are caused to take aluminum hydroxide only six times daily from the beginning, *i.e.*, one hour after meals, one hour after the interval feedings, and at bedtime Smith (1947) in a comparison of the reactive form of aluminum hydroxide (such as amphogel) and the non-reactive form (such as aluminoid), concluded that the outstanding advantages of the non-reactive over the reactive form are the ease with which it may be carried about by ambulatory patients, the lack of any taste and the decreased incidence of nausea and constipation in patients re- [illegible]

[illegible]

non-reactive form remains in the colloid aluminum hydroxide suspen- [illegible] the presence of hydrochloric acid for prolonged periods. Some men have substituted aluminum phosphate for aluminum hydroxide in this type of [illegible]

[illegible]

not furnish adequate proof that the ulcer patient who is maintained on a phosphorus-rich diet (*i.e.*, who is obtaining considerable milk and cheese) will experience a phosphorus deficiency as the result of using aluminum hydroxide as an antacid. Hoffman and Dyniewicz (1946) were unable to find any evidences that aluminum hydroxide affected the absorption of amino acids, ascorbic acid, vitamin A, glucose or neutral fat from the intestinal tract.

ALKALINIZED MILK DRIP

This is the original drip method, introduced by Winkelstein, of the Mount Sinai Hospital in New York, in 1931. The preparation employed consists of milk heated sufficiently to remove the chill and containing 5 gm. of sodium bicarbonate to the quart This is allowed to drip into the stomach at the rate of 30 drops per minute Originally the drip was administered continuously throughout the twenty-four hours for two or three weeks, but Winkelstein *et al.* (1942), reviewing ten years' experience with the method, said that in recent years the treatment had been modified as follows: the patient receives three liberal bland meals daily and atropine with the usual sedatives; one

hour after each meal the drip is started and it is continued until one hour before the next meal, even while the patient sleeps at night. More recently, Winkelstein (1944) has said that in mild cases the patients treat themselves only during the night. According to Winkelstein the milk drip is contraindi-

aluminum drip by some men is indicated in the report of Rush (1943), who used it in the Army as an adjunct in making the diagnosis of peptic ulcer, he found that patients with ulcer all experienced prompt relief from milk drip therapy but that patients with a functional gastro-intestinal disturbance almost uniformly failed to express more than transient relief of their symptoms upon the employment of this type of treatment

Protein Hydrolysate Therapy

Since Co Tui's (1945) report on the value of protein hydrolysate in the treatment of peptic ulcer there have been a number of other favorable reports and I have not seen one entirely unfavorable. But all of these reports are necessarily of a preliminary sort because not sufficient time has elapsed for a true evaluation of this new approach to ulcer therapy A typical recent report is that of Hodges (1947), who treated twenty-six patients who were selected for the study primarily on the basis of the chronicity of their ulcers, twenty-four of them having received adequate conventional dietary therapy previously on an ambulatory

institution of the protein hydrolysate therapy, the two others (making the total of twenty-six patients) had not been adequately treated in the usual manner but were included in the series because each had a chronic gastric ulcer the crater of which was nicely demonstrable in profile by roentgenogram, thus affording an opportunity to observe variations in its size with the progress of therapy. Twenty-three of the patients were hospitalized for the entire course of treatment, two were hospitalized for an initial four and seven days respectively, thereafter continuing on an out-patient basis, and one patient was treated entirely on an out-patient basis, being allowed to continue his work All hospitalized patients were allowed as much activity as they desired throughout the treatment The therapy consisted in the administration of a mixture in equal parts of protein hydrolysate (amigen) and dextri-maltose, between 650 and 800 gm dissolved in 2000 to 2400 cc of water being given

tinue the administration of 100 gm of protein hydrolysate daily in the form of

more frequently than each second hour for the first few days All twenty-

three patients from the start uniformly experienced more complete and longer relief from pain following the individual protein hydrolysate and dextrimaltose feedings than they had previously received from milk and cream or other bland foods Retention and vomiting disappeared almost immediately. In the three remaining patients the treatment was discontinued after two, ten and six days respectively, in one because a perforation was feared, in another because of a massive hemorrhage, and in the third because of the failure to obtain symptomatic relief.

Of the twenty-three patients who became asymptomatic, twelve showed no roentgen evidence of ulcer activity after the two to three weeks treatment period, eight showed marked improvement but with some residual irritability, spasticity or deformity (or both) and no demonstrable craters, and in three there was no radiographic evidence of improvement. A gain in weight was the rule, the average being 4 5 pounds, though one patient lost weight and two exhibited no weight change. Of the twenty patients in whom roentgen evidence of healing or improvement occurred, five had recurrence of ulcer symptoms within one to five months after termination of the therapy, one was subjected to a gastric resection in spite of the absence of recurrent symptoms because of partial pyloric obstruction, and fourteen had remained asymptomatic at the time of the report for from one to eight months.

The conclusion of Hodges from this study was that the beneficial effects of protein hydrolysate are ascribable to its buffering action and to the high nitrogen intake, and it was his belief that this type of treatment may become a useful adjunct to the medical management of peptic ulcer; but he felt that, as now employed, protein hydrolysate therapy will not prove to be a panacea

Miscellaneous Types of Therapy

Metz and Lackey (1940) reported good results following the supplementary employment of powdered posterior *pituitary* preparation as in diabetes insipidus, and in 1943 they brought their series up to 311 cases with a claim [illegible] In [illegible]

pendent findings of Emery and Schnitker were not nearly so favorable. [illegible] studies of Moersch *et al.* (1946), employing sixteen patients, did not encourage them to believe that *benadryl* will prove useful in treatment of peptic ulcer. Greengard *et al.* (1946), of Ivy's group, studied the effects of *enterogastrone* in fifty-eight patients and demonstrated the probability that the material is effective in preventing recurrences during the period of its administration and for an indeterminable length of time thereafter; but they were unable to explain the protection afforded on the basis of the action of enterogastrone in inhibiti[illegible] gastric secretion, and therefore the true nature of the effect remains as [illegible]ts of Spears and Pfeiffer (1947), and [illegible]d that some of the new *synthetic resins* may find a place in the treatment of peptic ulcer because they are innocuous and yet apparently highly effective acid removers. However, this matter is still in the stage of clinical experimentation

Treatment of Hemorrhage

The indications here are to combat shock, combat dehydration, prevent digestion of the clot and of the edges of the exposed blood vessel, promote

clot formation, restore the blood volume and maintain nourishment. In some instances resort to surgery is necessary.

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in shock. However, Nicholson and Miller (1941), and Schiff (1944), have opposed the use of these opiates because of their known tendency to produce nausea and vomiting, symptoms that one is trying to combat. The latter stressed the fact, previously brought out by others, that the relaxation in the tone of the duodenum occurring a few minutes after the administration of morphine might interfere with the constriction of an open vessel in the duodenal wall. He preferred phenobarbital.

Dehydration.—This condition is combated by proctoclysis or hypodermoclysis with saline or Locke's solution, or by the intravenous administration of dextrose It has not been proved that rectal administration of fluid stimulates gastric motor activity. These fluids only counteract dehydration; *i e*, they do not restore blood volume. Kirsner and Palmer (1939) strongly opposed the intravenous administration of any fluid in cases of massive hemorrhage, noting that in four of the five fatalities in their series intravenous fluids had been given. A frequent practice is to elevate the foot of the bed to "help the cerebral circulation"; Wood (1936) pointed out that venous return from the head may be so much impeded in this way as to contribute to the stupor by promoting cerebral edema.

Protect the Bleeding Area.—The employment of alkalis to prevent digestion of the clot through acid neutralization has theoretical justification and many men do so use them. However, Schiff (1944) said he was not convinced that alkalis were important in preventing clot digestion and that he used them only in the presence of pain

that nausea and vomiting are prevented and the patient kept remarkably

introduced, but Soper pointed out that no one criticized who had used the tube, in 1936, he (Thompson and Soper) reiterated his confidence in the method, but I have heard nothing of it since

Promote Clot Formation.—Quiet, of both body and stomach, is of course the chief measure here The application of an ice-bag to the epigastrium is thought by many practitioners to be of value; to me it seems that it can be of aid only in helping to hold the patient motionless Smithies (1935) and Andresen (1939), pertinently pointing out that such a measure only further chills a patient already in shock, preferred the opposite and more rational

alleged that this agent promotes clot formation and then protects the delicate fibrin from the action of strong unbuffered gastric juice.

Restore Blood Volume.—It is now almost unanimously agreed that transfusion of blood for the restoration of blood volume is indicated in many cases of hemorrhage. The continuous drip method is the one most frequently

TABLE 20.—MODIFIED MEULENGRACHT DIET (SCHIFF, 1944)

Time of Feeding	Food	Wt in Gm
	First and Second Day	
8 A M Breakfast	Orange juice	30
	Toast	20
	Butter	10
	Milk	75
	Cream	75
12 M. Dinner	Vegetable purée	60
	Pudding	100
	Cream	30
	Orange juice	30
4 P M.	Milk	75
	Cream	75
	Fruit purée	60
	Pudding	100
	Cream	30
6 P M Supper	Bread	20
	Butter	10
	Fruit purée	60
	Pudding	100
	Cream	30
	Milk	75
	Cream	75
10 A.M 2 P M. 8 P M	Eggnog	
	Milk	150
	Egg (1)	50
	Sugar	5
	Soda cracker (1)	
	Butter	5

Milk and water in volumes up to 5 oz are allowed between feedings as frequently as patient desires

[illegible] blood is given at the rate of 90 to 150 cc. per hour, which [illegible]

5 grams per 100 cc. (less than 35 per cent), a red count of two million or less, systolic blood pressure of 90 mm. or less, a blood urea nitrogen of 50 mg per 100 cc. or more or a persistent elevation or rising concentration, delirium or persistent headache, marked restlessness uncontrolled by other means, and general "poor appearance"

Black and Smith (1941) found that plasma transfusions affected their patients adversely.

Maintenance of Nourishment.—Most internists have now embraced the viewpoint that an empty stomach is never at rest and that it should be kept at least partially filled from the beginning with food that combines readily with

TABLE 20.—*Continued*

	Third day on	
8 A M Breakfast	Orange juice	30
	Strained cereal	90
	Cream	60
	Toast	20
	Butter	10
12 M Dinner	Minced meat	60
	Mashed potato	100
	Vegetable purée	60
	Toast	20
	Butter	10
	Fruit purée	60
	Milk	90
	Cream	90
	Orange juice	30
4 P M	Milk	180
	Chocolate paste	*20*
6 P M Supper	Cottage cheese or minced meat	60
	Bread	20
	Butter	10
	Pudding	100
	Cream	30
	Milk	90
	Cream	90
	Orange juice	30
10 A.M	Eggnog	
	Egg (1)	50
	Milk	150
	Sugar	5
	Soda cracker (1)	
	Butter	5
2 P M 8 P.M	Eggnog	
	Egg (1)	50
	Milk	150
	Sugar	5

given at two-hour intervals beginning at 8 A.M. and ending at 8 P.M. Between feedings the patient is allowed water or milk in quantities up to 5 ounces as desired. Schiff's modification of the Meulengracht diet is presented in Table 20.

There are many reports of the satisfactory employment of the full feeding regimen in bleeding ulcers but of course it is not successful in every case. In their appraisal of various methods of treatment, Rafsky and Weingarten (1942) were able to follow the regimen without interruption in twenty-six of the thirty-nine patients in whom it was tried; discontinuance was due to the following factors: recurrence of bleeding in seven patients, three of whom died; severe pain in three, one of whom had a perforation of his ulcer and died postoperatively; and severe nausea and vomiting in three. Wheeler (1943) has pointed out that the principal advantages of full feeding are that the patient seems to get more prompt relief of pain, the bleeding apparently stops just as quickly, and the stay in hospital and the time required to bring the blood count back within normal [illegible]

whose board-like rigidity of the abdomen presents frank evidence of perforation, he recognizes the following criteria for impending perforation—a history of unusually severe and persistent pain, particularly marked tenderness on abdominal palpation, undue fever or leukocytosis, or the finding of penetration in recent roentgenologic studies of the gastro-intestinal tract.

Resort to Surgery.—Surgical statistics are not in complete agreement regarding indications for intervention, which likely means that medical and surgical judgment must still weigh each case separately. Heuer (1946) said, as a result of a study of 337 patients admitted because of massive hemorrhage due to peptic ulcer, that if operation to save life is decided upon it should be done within twenty-four or forty-eight hours of the onset of hemorrhage; in his series the mortality in patients operated on early was 10 per cent whereas that of patients operated on late (after forty-eight hours) was 70 per cent. However, it seems to me that Martin (1943) made a very important point in stressing the fact that patients who are seen on a surgical service are much more likely to be in a most serious condition because they have either been transferred from a medical service where they have bled severely or long or they have been admitted from the accident ward where the bleeding is usually dramatic, either as to the speed or the total amount; one can expect the mortality from hemor- [illegible] on the medical wards to [illegible]

that an elective operation should not be advocated for patients who have recovered from hemorrhage unless they have associated pain, patients operated upon for painless and massive hemorrhage being frequently readmitted with subsequent massive hemorrhage even after subtotal resection. Wangensteen (1947), of the University of Minnesota Medical School, said that the decision whether or not to operate is not easy to make and that oftentimes the operation itself is technically very difficult. I think that even those surgeons who hold out for Finsterer's "first forty-eight hours" as the optimum period for surgical attack will agree that young individuals with bleeding ulcers rarely die and that when they do it is usually as a result of complications rather than exsanguination.

Treatment of Acute Perforation

Acute perforation demands immediate surgical intervention Most patients recover who are operated upon within six hours after the perforation has occurred, for each hour after that time the chances of death are greatly

in 28 per cent, good in 27 per cent, fair in 22 per cent and poor in 23 per cent of the cases.

COLON CONSCIOUSNESS

(Constipation, Mucous Colitis, Unstable Colon, Spastic Irritable Colon, Visceroptosis)

This condition can no longer be satisfactorily presented as comprising several distinct entities each resting upon its separate pathologic basis, for the unity of the functional disorder underlying them all has now been firmly established. It is primarily a disturbance of the conditioned reflex upon which normal defecation depends, characterized by changes in colonic tone, irritability and secretory activity, induced by environmental imbalance in a neuropathic individual, aggravated by "treatment," and expressed as awareness of the colon and its activities. The normal physiologic behavior of the colon and rectum is quite simple. When a meal is taken the ileocecal valve is relaxed and the contents of the ileum are propelled by peristaltic action into the cecum and ascending colon. Simultaneously, waves of contraction sweep along the colon to convey the contents into the pelvic portion, haustrations (segmental movements) at the same time serving to effect intimate contact with large surfaces of the mucosa so that water is absorbed and the feces converted into their final form. In the infant there is no mental control of the terminal stage of this stuffing process, a lack with results that are well known. But in the course of time—I am following Hurst closely at this point—an elaborate

abdominal wall are voluntarily contracted, and contraction of the rectum with relaxation of the anal sphincter permits the feces to be evacuated. In most adults this scene is enacted diurnally, but not in all, for there are many individuals who skip one or several days and are not in the least disturbed provided their absorption with life is properly extroverted. The colon-conscious fellow is troubled, though! For not only does he come complaining of the number of days he has failed to have an evacuation, but he knows that the stools, when they do oblige him, are ribbon-like, pencil-shaped, accompanied by much mucus, and so on; and he clamors for the opportunity to tell about these things to assist the doctor, whose mind's eye is of course ever steadily fixed on the standard stool encased with the meter bar in Paris. More often than not he is also wedded to the fascinating idea of "autointoxication," about which faddists (not all outside the profession) and the daily newspapers hold forth with unremitting gusto; so that many times the stool he tells about is really only dimly remembered, since for months or years he has kept himself satis-

fyingly mushy, or even in a state of chronic diarrhea, with drugs. Or the bowel

colonlike structure; sometimes there are paroxysms of severe abdominal colic. "Visceroptosis" is a term that has

strous binders and by night with prodigious exercises in the bed, the latter usually culminating, I believe, with a slide down onto the abdomen from the knee-chest position so that everything will remain safely tucked up during the long dangerous night.

THERAPY

In an ancient recipe for rabbit stew one is enjoined to "first catch your rabbit." How sound that advice is when applied to the subject in hand; first be sure that the patient before you is suffering from simple colon consciousness before you undertake to treat him. Gynecologic, proctoscopic, sigmoidoscopic, roentgenologic, internologic (if I may coin the word) examinations may reveal many primary or secondary organic causes for the syndrome: adhesions, pres-

or pancreas; and so on. There are many resemblances between allergic states and the condition of being colon conscious, especially in those instances in which the symptoms are of intermittent and spasmodic nature. Should it be possible to determine the offending substance and to eliminate it from the diet, or environment, or even to desensitize the patient to it, much misery will be avoided and a near-miracle performed. The matter does not find such simple allergic solution nearly so often as could be desired; still, any case may always be the lucky one In summary, then, the patient must be given the benefit of thorough examinations of all sorts, and only if these are convincingly negative is he to be assigned to the group under present consideration.

Psychotherapy.—There seems to be little difference between patients suffering from one or more forms of "indigestion" and those bothered by awareness of the colon and its performances, save that the latter center their disturbances lower in the tract. All of these individuals need readjustment to something in themselves or in their environment. It is the practitioner's duty to find that something, then to lead the patient to face and live with it. I know nothing easier to set down in a few words!

Habit and Defecation Posture.—The stool should be visited by every person every morning after breakfast. Too often housewives who are busy at this time, and men who take their breakfast at a quick-lunch counter en route to the office, "put it off" until the desire is no longer felt. After the conditioned reflex has become dulled through such disregard and "constipation" has set in, if one impresses the necessity of the regular daily visit upon these people they often accept the advice and carry it out with a grim determination which easily defeats their purpose, for defecation is accomplished only by the maintenance of a nice balance between contraction *and* relaxation. A few puffs of a cigaret, a few peeps at a newspaper or magazine, is a recipe well known to

many persons. Sometimes placing the feet upon the round of a chair so that the thighs are flexed on the abdomen is helpful; the principle is anatomically, physiologically and traditionally sound—surely the early morning sun the world around still catches the majority of mankind squatting upon its heels at this daily duty. In infants one must also reckon at times with lack of ability or desire to use the expulsive forces necessary for defecation.

Exercise.—Bodily exercise is of value in the promotion of general well-being, and if it can be taken in the form of some competitive game in which the maladjusted hypochondriacal patient will lose himself for awhile, may be counted upon to be of considerable assistance in the treatment of these cases. But in and of itself it probably has little value; even letter carriers, who could never be rightly accused of a sedentary existence, are said to be a constipated lot Massage of the abdominal muscles, or rolling a heavy ball about over the

... nowadays frowned upon because of the danger of doing injury ... these measures ... a number of patients

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... a colon

regimen ... ysicians

what might ... the dry hard ... of the colon and the dry hard ... than that. However, ... quarts of water

consciousness is much farther down than that. However, ... several quarts of water recommend that their constipated patients take several quarts of water daily. Some patients like to add ordinary table salt to some of this water and others put in some sauerkraut juice Persons who treat themselves in this way must have happy lives shuttling between the water cooler and the conveniences.

Diet, Bran, Agar, Psyllium, Metamucil, Karaya Gum and Beet Pulp.—Present belief is that the colon of the patient suffering from functional disturbance of the organ is practically always in a spastic state due to hyperirritability, and that the best thing to do for such a colon is to give it rest by the use of a smooth diet (see Nervous Indigestion). The rational thing is ... off his beloved cathartics and enemas and wait to see ... smooth diet, in some instances it will be ... diet provides,

t ... n has been

... onstipation

... reful study,

in others not, ... allowed to fill after the punishment ... has fallen down under ... into two types, spastic and atonic, has fallen down under ... the atonic and with it has gone the conception that the chief trouble in the atonic variety was that the patient ate too little roughage and therefore needed to gorge himself on such things as lettuce, celery, endive, spinach, carrots, beets, string beans, figs, dates, raisins and prunes. It is true, as already said above, that some individuals seem to need more bulk in the bowel than others, and the above foods provide this nicely, but such individuals are certainly in the minority and there is now believed to be little justification for excessive roughage feeding of every person in whom roentgen study after a barium meal or enema shows evidences of decreased colonic tone. An occasional patient will get a nice effect from a small amount of bran in the form of cookies, muffins, bread, cakes, or taken with sugar and cream to replace the morning cereal, but leading gastro-enterologists are now firmly opposed to its use in most cases since it robs any diet of whatever property of "smoothness" it may have had. Certainly all in ... duals should be warned

against using bran on the principle that if a little is good a lot is better; it is not surprising that there are on record one or two instances in which silly individuals have actually stuffed the gut with this dry material until they produced obstruction. Some observers have found that bulk can be satisfactorily provided without irritation through the use of 1 or 2 tablespoonfuls of ordinary x-ray barium taken in water two or three times daily; 1 to 2 tablespoonfuls of beet pulp have given satisfaction in some cases. Some colon-conscious patients are made worse not only by the physical irritation of roughages but also by the fact that they suffer from excessive intestinal fermentation (see Index) and they therefore react to these cellulose materials by the production of large amounts of gas. Agar passes through the intestinal tract without undergoing bacterial digestion and merely softens and adds bulk to the feces by virtue of its property of retaining water. It is best used in the form of shreds or a coarse powder, for when finely pulverized it too may produce colic, according to Fantus. It is usually employed in several tablespoonful doses incorporated with foods at the table. Psyllium is a small brown seed that exudes a considerable amount of mucilaginous material when it is moistened. The dose is 2 to 4 teaspoonfuls stirred up with twice as much hot or cold water until a gelatinous mass is formed, which is then spread on bread or taken with cream and sugar, with stewed fruit, or in soup; some people like to place the seed in fruit juice and drink the mixture with mastication. A mixture of psyllium and agar is commercially available ... cent mixture of dex- ... teaspoonful of meta- ... three times a day and followed with a large glass of water. Thienes and Hall (1941) found that psyllium caused pigmentation of the kidneys in experimental animals, but that neither in these animals nor in nine patients who were long-time users of the agent did it cause any evidences of damage to renal function. Karaya gum, which absorbs and holds a large quantity of water in the tract, is the newest of the agents of this type which exert their effect by physical rather than chemical action, it seems to cause intestinal irritation in some instances, and Alvarez (1940) reported a case in which migrainous attacks were attributable to the use of this agent.

... is to break a vicious ... must at least be approa... l enema must ... otherapy plus cessation of routine dosing, to bring about normal evacuation, it is well to bear in mind that a pint of cool water containing a teaspoonful of sodium chloride or sodium bicarbonate is to be preferred to the ordinary soap-suds enema, which is so irritating to even the normal bowel that for some time after its use the mucous membrane presents an angry red appearance. Perhaps it is more rational to inject a small amount of oil at night as a retention enema; about 3 ounces (90 cc) of cotton seed oil or liquid petrolatum, warmed, olive oil is likely to be irritating. The older custom of injecting large quantities of oil upon retiring, and to make an elaborate ritual of the procedure, is no longer in favor If the feces have already become impacted, the reader should bear in mind that the injection of water, not oil, is indicated. When use of an irri-

tant is actually required, Levy has employed a mixture of 5 cc. of rectified oil of turpentine, 25 cc. of cotton seed oil, 45 cc. of glycerin and 45 cc. of soft soap. One to 2 teaspoonfuls of this mixture are added to 4 ounces (120 cc.) of water and injected into the rectum by means of a rubber bulb syringe. The action is quick and complete only because this concoction is violently irritating.

Suppositories.—Graham pointed out some years ago that if rapid evacuation of the rectum and colon is desired, a 5-grain (0.3 gm.) quinine dihydrochloride suppository will promptly produce a large but not watery stool. Glycerin suppositories have of course been in use since time out of mind.

Colonic Irrigation.—Bastedo is perhaps the principal champion in this country of the use of colon irrigations in so-called "mucous colitis"; Friedenwald and Morrison, and a few others, favor the method also But the vast majority of those who confine their practice largely to gastro-enterology flay the procedure as being based upon an entirely erroneous conception of the nature of mucus secretion in the bowel. Hurst pointed out that the mucous membrane of the colon, like all other mucosae, secretes mucus as a response to both mechanical and chemical irritation as a sign of healthy activity. The

nation for the phenomenon. "A boy of 18 has always had a tendency to constipation and had been continually dosed by his mother with aperients His report stated that he had been given an irrigation of 30 pints, the treatment lasting one hour and ten minutes 'The first 12 pints brought away loose faeces but no mucus, but after that a large quantity of jelly mucus was passed continuously until the end of the treatment.' That is to say, 12 pints of fluid were required to irritate the healthy mucous membrane of this boy sufficiently to produce excess of mucus, but when once it began to be secreted it naturally continued, and there would still have been mucus present if he had received 100 instead of 30 pints

"The patient is often told that the mucus has been accumulating in his colon for weeks or months and that is why he has never seen it in his stools, whereas the truth is that his mucous membrane is none the worse for a few pints of water, but after the first few pints it has to protect itself by secreting mucus. It is sometimes reported that by the end of the patient's 'cure' little or no mucus is present, the explanation being that the patient's mucous membrane responds at first by the secretion of mucus to the unaccustomed irritation, but after some weeks the mucus-secreting cells become exhausted and go on strike" Soper has maintained that if irrigation is continued long enough, the "foul-smelling material" described by Bastedo can be secured in persons having a normal colon, being in his opinion the normal contents of the ileum changed by the treatment. Krusen reviewed this subject for the Council on Physical Therapy of the American Medical Association, in 1936; it is difficult to find anything very commendatory in his report.

Bastedo's Technic.—The irrigation is given from a height of 2 feet, using either a No 34 French tube, velvet-eyed with a closed end, inserted about 6 inches, and used for both inflow and outflow of the fluid after the colon has been filled to capacity, or employing the two-tube method in which a 20 to 24

French soft rubber velvet-eyed catheter is inserted 6 inches for inflow, and a 30 or 32 French velvet-eyed closed-end rectal tube (or stomach tube) inserted 3 or 4 inches for outflow. The tubes are inserted about fifteen minutes after an evacuation enema of plain water has cleared the rectum and lessened the chances of disturbances from defecation reflexes. Plain water, slightly above body temperature, is used, usually 6 to 10 gallons in the course of an hour, the first gallon with the patient on the left side with knees drawn up in order to clean out the lower colon, then for the remainder of the time on the back in order for the fluid to reach the cecum. Saline would make the patient very thirsty, and it is doubtful if the vaunted ability of sodium bicarbonate to dissolve mucus outweighs the disadvantages of its stimulation of the kidneys, disturbance of acid-base balance and tendency to cause gas and colic. These irrigations are usually employed every day or two for a week, then every three or four days for several weeks longer, and then once a week for as long as considered necessary.

Cathartics.—The following drugs are discussed because I have not as yet the courage to omit them,
from the matter presented
weans his patient away fr
colon consciousness.

Cascara Sagrada.—This drug is a mild yet reliable cathartic, though one occasionally finds a patient in whom it fails to act. When there is complaint
that it is being taken in overdose.
stool
dose
of the aromatic fluidextract necessary to accomplish this ... chms (4–12 cc.), taken before meals and at bedtime, or all in one dose at bedtime The following prescription in which there are 20 minims (1.2 cc.) of the aromatic fluidextract to the teaspoonful, offers cascara in a pleasant vehicle; the tincture of nux vomica, so often given with cascara, is omitted here because I believe its inclusion to be irrational and dangerous from the standpoint of the poisoning of young children getting hold of such bottles.

℞ Aromatic fluidextract cascara sagrada	℥x	40 0
Syrup cinnamon	℥x	40 0
Water to make	℥iv	120 0

Label 1 teaspoonful one-half hour before meals and upon retiring.

This dose may be doubled or trebled if necessary, but it should be borne in mind that with cascara it is sometimes possible after a while to reduce the dosage gradually without losing effect. Fantus offered the following dosage of the aromatic fluidextract for children.:

	Cc.
Child, 6 months old	1
Child, 18 months old	From 2 to 3
Child, 3 years old	4
Child, 5 years old	From 4 to 8

The adult dose of the plain fluidextract is 15 to 60 minims (1–4 cc.), but this preparation is so bitter that it seems needlessly cruel to prescribe it for adults, and children can hardly be made to take it at all.

Senna.—This drug is more powerful than cascara sagrada and also much more prone to cause griping and general abdominal soreness; it is definitely

contraindicated if there is intestinal inflammation of any sort. The dose of the fluidextract is ½ to 1 drachm (2–4 cc.), if taken at one time, or 8 to 16 minims (0.5 to 1 cc.), several times daily. Four to 8 minims (0.25–0.5 cc.) of the tincture of belladonna added to each dose will antagonize griping. The U.S.P. syrup has a full dose of 2 drachms (8 cc.). Such nostrums as "castoria" and "syrup of figs," which owe their chief value to senna, should not be used. Senna may also be pleasantly taken as the N.F. compound glycyrrhiza ("licorice") powder; adult dose, 1 drachm (4 gm.) or more, stirred up in water.

Dosage of compound powder of glycyrrhiza for children (Fantus)

Age of child	Gm.
6 months	0.60
1 year	0.90
2 years	1.20
3 years	2.00
5 years	3.00

Aloe.—The griping tendency of aloe is notorious. The N.F. pill contains 2 grains (0.13 gm.) and the official dose is 2 pills, which is likely to be too large. Fantus offered the following prescription:

℞ Powdered aloe	gr xxiij	1.5
Powdered soap	gr xxiij	1.5
Mix. Make a mass and divide into 30 capsules		
Label: 1 three times a day after meals		

The active principle, aloin, should be reserved for use only when excessive action is needed; it may be given in a capsule containing ¼ grain (15 mg.).

Phenolphthalein.—This is a yellowish-white, odorless and practically tasteless powder, which has one great fault, namely, that a small dose sometimes acts excessively while a large dose may at times fail to act altogether. Upon the whole, however, the drug is very reliable. It is usually given at bedtime and in the morning produces a stool very much like the normal. The adult dose is from 1 to 3 grains (0.06–0.2 gm.); infants of eighteen months may be given as much as ½ grain (30 mg.). The National Formulary contains a cocoa and sugar flavored tablet containing 1 grain (tablets of phenolphthalein, N.F.). A great many nostrums rely upon phenolphthalein for their principal or sole active cathartic ingredient; they are for the most part pleasing preparations, but there is no good reason why the physician should not prescribe the drug in its Formulary preparation. A sufficient number of skin eruptions have been shown to be due to the use of phenolphthalein to warrant one in taking this possibility into account in urticarias and erythemas; general constitutional effects, in which circulatory, renal, or nervous disturbances predominate, are much less often reported. Abramowitz thoroughly reviewed the work of himself and others on the subject, in 1935, and his paper, as well as the discussion which followed its reading, leaves little doubt that the reactions are allergic in nature. However, the ordinary acute toxicity of phenolphthalein seems to be extremely low. Blatt *et al.* (1943) reported four cases in children from two to three and one-half years of age who had ingested up to 15 grains (1.0 gm.) without manifestation of either immediate or delayed toxic reaction. Fantus and Dyniewicz, and Steigmann *et al.* of the same group, in studies between 1936 and 1938, showed that phenolphthalein is not excreted in the milk of nursing women, apparently does not disturb liver function, and would

condition in a previously normal bowel, though I wonder how accurate the latter statement is.

Salines.—*Magnesium sulfate (Epsom salt)*: Very effective but objectionable in taste, which may be largely overcome by dissolving the salt in one of the palatable fruit juices. A dose of ½ to 1 ounce (15–30 gm.) is quite large enough *Magnesium citrate*: principally used as the solution of magnesium citrate which is available as an effervescing preparation in 12-ounce (360 cc) bottles; dose, 1 bottle or less; nauseating to many people and often quite violent in action. *Milk of magnesia*: palatable and easy to give to children; also an antacid; laxative dose, 2 to 4 drachms (8–16 cc.) taken from the spoon or stirred in cold water; addition of fruit juice converts it in part into magnesium citrate which is more active (see above). *Sodium sulfate (Glauber's salt)*. dose ½ ounce (15 gm); extremely nasty. *Effervescent sodium phosphate*. mild but fairly pleasant; dose, 2 to 3 drachms (8–12 gm.) in water. *Compound effervescing powder (Seidlitz powder)*: dose, the contents of one blue paper (sodium bicarbonate and Rochelle [potassium and sodium tartrate] salt) and of one white paper (tartaric acid), dissolved separately in water and then mixed; *fairly pleasant in taste*. *Sodium chloride*: many individuals take about 1/3 teaspoonful of common salt in a glassful of hot water on arising and repeat the dose once or twice while making the toilet, claiming a good cathartic effect; this is supposed to be very clever and to teach us doctors something, I have been informed.

Liquid Petrolatum.—Liquid petrolatum is bland, odorless, tasteless, and colorless, and can be taken from the spoon by most patients without any difficulty. It can be easily flavored, however Hinton found that in 500 cc. of the oil any one of the following flavoring oils is satisfactory: anethol, 10 drops; oil of almond, 15 drops; oil of cloves, 10 drops; oil of cinnamon, 5 drops; oil of peppermint, 15 drops; oil of spearmint, 15 drops; and methyl salicylate, 25 drops. Fantus suggested that the oil combination used in the flavoring of aromatic elixir might be used to make liquid petrolatum aromatic; a combination of this sort would be oil of orange, 2 cc.; oil of lemon, 0.5 cc.; oil of *coriander, 0.2 cc.; oil of anise, 0.05 cc.; and liquid petrolatum, 1000 cc.*

arations, Fantus wrote: "The worst that can be said about them is that they are more expensive than the same quantity of liquid petrolatum, containing as they do from 25 to 60 per cent of the active agent. The dose of 1 tablespoonful is recommended for them with the suggestion that the activity of the emulsified oil is greater than that of the plain oil, a statement that remains to be proved."

Morgan, in a paper read in the Section on Gastro-Enterology and Proctology at the 1941 meeting of the American Medical Association, severely castigated liquid petrolatum as a cathartic. His charges were that: (a) it keeps the rectum partially full most of the time, causing its conversion into an abnormal receptacle for fecal material; (b) complete evacuation of the rectum is impossible for there always remains a tenacious layer of a dirty mixture of oil and

feces covering the rectal mucosa; (c) absorption of carotene, and to a lesse extent of vitamins A and D, is seriously interfered with; (d) digestion is incomplete because the passage of the contents through the bowel is hastened; (e) the healing of postoperative wounds in the anorectal region is delayed; (f) leakage from the anus may give rise to pruritus ani; (g) liquid petrolatum may be absorbed and cause pathologic changes in the abdominal viscera. It will be very interesting to see how well this thoroughgoing indictment will be upheld with the passage of time.

Treatment of Colic.—Morphine or dilaudid is of course contraindicated here because of the frequent recurrence of the attacks; it should be remembered that the new drug, demerol, is also addictive. Bastedo finds that castor oil by mouth and a hypodermic of codeine phosphate, ½ grain (30 mg.), and atropine sulfate, 1/65 grain (1 mg.), plus hot applications to the abdomen in the form of a hot water bag, electric pad, poultice or stupe (for method see Pneumonia), or a hot bath, will be followed by relief and sleep in most instances. If this fails, however, he irrigates, and if relief is still not obtained, puts the patient in the knee-chest position and slowly injects into the colon ½ to 1 pint (250–500 cc.) of warm olive or cotton seed oil, the injection often being followed after a few hours by the passage of an abundance of mucus and the disappearance of the colic.

In some cases of colon consciousness there may be more or less constant pain though true attacks of colic do not appear, atropine sulfate, or the extract or tincture of belladonna in comparable dosage, is used by many men in such instances, giving the drug three or four times daily for five or six days and then allowing the same number of days to elapse without it.

NONSPECIFIC ULCERATIVE COLITIS

Ulcerative colitis is characterized by inflammation of the mucous membrane and walls of the large intestine, in the pathologic picture of which ulceration predominates. This ulceration usually begins in the rectum and spreads upward eventually to involve the entire colon. It may, however, affect any one part, or several separated parts, of the tube. The course is in most cases a chronic one, extending over months and years, but the symptoms are not usually continuous during this time for there are often long periods of remission between severe attacks of the malady. The symptoms are fever, malaise, prostration, protracted and persistent diarrhea with some tenesmus, and the passage of blood, mucus and pus. Distress from gas, and griping and other sensations along the course of the colon, are often experienced. Much weight is lost, a peculiar gray pallor is common, and in very severe cases the body has a peculiar odor and the face a hopeless expression. Pollard *et al.* (1947), of the University of Michigan Hospital, found anemia present at the time of admission in seventy-one of 100 cases. In fifty-eight of the seventy-one cases the anemia was hypochromic-mycrocytic, in the other thirteen cases normocytic, and hence in none of the cases macrocytic. Bargen has described a diplostreptococcus as the causative agent in many cases of the disease, but there are few who agree with him, the very thorough study of the fecal flora in ten cases, performed by Rodaniche, Palmer and Kirsner (1943), revealed *Streptococcus fecalis* as the predominating streptococcal species in the feces and the only streptococcus found constantly in all the cases. Dack *et al.* considered *B.*

study indicated that the assumption is probably gratuitous with regard to *E. coli* at least. *Endamoeba histolytica* and *Balantidium coli* have not been overlooked, but most observers feel it entirely unlikely that these parasites can be convicted. Henderson *et al.* (1942) reported a case of histoplasmosis of Darling in which the syndrome of ulcerative colitis presented, and they therefore stressed the importance of examination of stools for the presence of *Histoplasma capsulatum* in all cases. Many men in this field hold with the late Sir Arthur Hurst, in England, and Crohn and Rosenak, and Felsen, in this country, in the belief that ulcerative colitis is a form of chronic bacillary dysentery. Felsen and Wolarsky (1947) reported that in 9.8 per cent of sixty-

not seem to be contagious, for Jackman's (1942) study of the records of 900 cases at the Mayo Clinic revealed occurrence in more than one member of a family in only 1.8 per cent of the series. Mackie's observations a few years ago

of Ginsberg and Ivy (1946) that in most cases nutritional deficiency is secondary and that there is no evidence indicating that the disease is due to a disturbance of the excretory function of the colon. They said further that there is a paucity of evidence showing that chronic ulcerative colitis is a late stage of mucous colitis, or of functional dyskinesia of the colon, or of some subtle vascular, neurotropic or metabolic disturbance. Rowe (1947) said that he and his associates have accumulated evidence that chronic ulcerative colitis is often

cause of the disease.

THERAPY

Psychotherapy.—Daniels (1944), who has apparently examined quite a number of these cases psychiatrically in several New York hospitals, says that

ease, that these patients are emotionally immature, that they frequently break at crises which represent a forward step in emotional sexual maturity such as engagement, marriage and childbearing, that financial difficulty and loss of a close relative are frequently important, that fixation on the mother is

severity of the neurosis and the experience and equipment of the therapist. But it seems to me that the disheartening feature of the psychotherapeutic approach is implicit in West's (1946) statement to the effect that unless the

patient can be brought to a profound new understanding of himself, or unless one can tap an unfailing source of new confidence within his own mind, the temporary relief of anxiety induced by the physician's self-confident explanation is unlikely to cause more than transitory relief of any complex psychosomatic disorder.

Rest.—It would seem that all authorities, whatever their disagreement on other points, are unanimously of the opinion that the patient should be maintained at complete rest in bed so long as there is fever and more than two or three stools daily.

Diet and Vitamins.—Donald and Brown (1940), of the Mayo Clinic, said with regard to victims of this disease that one fundamental fact is certain· their chances for recovery depend greatly on the availability of the best possible quality of food. They found that protein is the most important article, chiefly in the form of red meats, liver, kidneys, sweetbreads and lean pork, and that since fruit and vegetables may add too much residue to the diet and increase the number of bowel movements, restriction of these articles requires the supplementary use of ascorbic acid and all the fractions of the B complex.

tion of liver extract as in pernicious anemia, believing that the effective factor is probably some as yet unidentified substance in liver. As a result of their exhaustive study of thirty-seven patients, Bercovitz and Page (1944) came to the conclusion that the syndrome of chronic ulcerative colitis is not confined to an altered physiology of the colon but is also manifested by altered absorption and utilization, an impairment of the insulin mechanism, generalized decreased capillary resistance and altered blood coagulation by a decrease in prothrombin content In some of their patients with rectal bleeding treatment

and King (1946) reported the intramuscular employment of penicillin in a small series of cases with results indicating that such therapy might be of

cedure as ileostomy without the disadvantages of the latter. Streicher (1947), as the result of the employment of penicillin concomitantly with sulfathiazole in forty-five patients, felt there was some reason to believe that the combination of drugs, both being given by mouth, could be used with advantage.

Vaccines, Antivirus and Serum.—Felsen (1945) prepares vaccines from autogenous dysentery strains and from other organisms that he considers "secondary" invaders and combines these with polyvalent strains of the same organisms recently isolated from many other patients. During the time that this vaccine is being administered an antivirus of a modified Besredka type is given by rectum Bargen has prepared a vaccine with the organism that he considers causative and has also used a serum prepared by immunization of the horse

Diarrhea.—Early in all cases some attempt is usually made to control the diarrhea, though it is a fact that such success as rewards these efforts is nearly always only temporary. The following drugs are usually tried out in succession:

- Bismuth subcarbonate, 20 to 30 grains (1.5–2 gm.) every three hours
- Bismuth betanaphthol, 10 grains (0.6 gm.) every four hours.
- Calcium carbonate, 15 to 30 grains (1–2 gm.) every four hours.
- *Calcium* glycerophosphate, 10 to 15 grains (0.6–1 gm.) every four hours
- Acetyltannic acid (tannigen), 3 to 10 grains (0.2–0.6 gm.) every four hours.
- Protan, 20 to 30 grains (1.3–2 gm.) every two hours.

Colic.—During the course of a severe attack, hot stupes applied to the abdomen, according to the method described under Pneumonia, often bring relief; morphine, 1/8 to 1/4 grain (8 to 15 mg.) or dilaudid 1/48 to 1/32 grain (1.3 to 2.0 mg.), *or preferably codeine 1 grain (60 mg.), may be needed;* of course paregoric in usual doses could also be used. Hurst gave tincture of belladonna (laudanum) every four to six hours, increasing from 5 minims (0.3 cc.) to the maximum amount that can be taken without uncomfortable dryness of the mouth resulting He found a tablespoonful of charcoal several times daily also helpful. Bargen and Jackman (1939) found that the addition of 1/3 grain (20 mg.) of papaverine hydrochloride to an opiate-atropine mixture is helpful.

means of antiseptic enemas
or of the ulcers. It should be
rei e to trauma in colitis, and
overloading with excessively large retention enemas should therefore be avoided, and the soft catheter should be introduced only just beyond the anal sphincter. Eyerly and Breuhaus (1938) followed a cleansing enema in one hour with a retention enema consisting of 3 to 5 ounces (90–150 cc.) of 3 per cent *aluminum hydroxide and 15 per cent kaolin in colloidal suspension* mixed with an equal amount of sterile distilled water, the patient retaining this as long as there is no discomfort. Best (1936) used daily rectal injections of 2 to 4 ounces (60 to 120 cc) of cod liver oil.

Intestinal Oxygenation.—Felsen (1945) has for some years been studying the effects of altering the gaseous tension in the intestines by the rectal introduction of oxygen. Passage through warm water heats the gas, which is then allowed to enter through an ordinary soft rubber catheter introduced only a few inches; small divided doses are given three to seven *times daily,* the total daily dosage being 250 to 2000 cc. The patient may be in the upright posture, on the toilet seat, or in the recumbent position in bed. There is moderate distention of the bowel as far as the pylorus, but much of the gas is apparently rapidly absorbed since very little is ejected from the rectum Felsen believes that this treatment leads to the diminution of spore-bearing anaerobes, encourages the superficial growth of obligatory or facultative aerobes, and favors a homogeneity of intestinal flora; the effect of oxygen on

years ago reported
ses. Early in 1947,
red treatment con-
sists in the giving of calcium lactate, 30 grains (2 gm.), or calcium gluconate, 60 grains (4 gm.), orally three or four times daily, three and a half to four hours after meals, the patient being cautioned not to eat between meals

Parathyroid extract is injected intramuscularly in dosage of 100 to 150 units at intervals of forty-eight to seventy-two hours for two or three doses

[illegible]

because of low blood pressure. The normocytic anemias responded temporarily to transfusions, but a sustained cure of the anemia was dependent on the cure of the toxemia, infection and malnutrition that produced it. Benson *et al.* (1942) said that at the Mayo Clinic they felt these chronic ulcerative colitis patients were more liable to transfusion reactions than ordinary postoperative or anemic patients.

Allergic Factors.—Rowe (1947) said that in fifty-two hospital cases and eighteen office cases, good or excellent results had been accomplished in fifty with the control of food allergy. However, Mackie (1942), while believing allergy to be very important, thought it often only a secondary factor, *i e*, a local sensitization developing upon a tissue previously inflamed through the operation of some other factor.

Surgery.—Streicher (1942), in summarizing his own experience and that of one hundred specialists whom he consulted by questionnaire, stated the opinion that ileostomy should be performed only upon those patients in whom the colon has undergone irreparable damage Kleckner (1947), among others, advocates the following of ileostomy by two-stage colostomy within two or three months He says this measure provides cure, and that with time and full cooperation on the part of the patient as to diet and local care (but with the necessity of wearing a bag), health can be restored to patients whom medical treatment alone has failed to cure Marino (1947), in discussing Kleckner's paper, said that the more ileostomies he had performed the more he had wished that there was some other method of taking care of these patients, he expressed the hope that the antibiotics might take the place of this operation in some of these desperately ill patients. Appendicostomy or cecostomy are procedures that seem to be much more favored in England than in the United States. Bargen *et al* (1943), in presenting a summary of experience at the Mayo Clinic, suggested that when it has become necessary to perform ileostomy the advisability of a subsequent colectomy should be seriously considered.

HEMORRHOIDS

Internal hemorrhoids are masses of redundant tissue caused by the dilatation of capillaries, arteries, or venules just inside the anal sphincter. They cause trouble either by reason of the fact that they are ulcerated and thus give rise to considerable pain when scraped by the feces, or by their bleeding, or by their prolapsing, which necessitates frequent manual replacement up behind the sphincter, or by the fact that they become strangulated after having passed out through the sphincter The so-called "external" hemorrhoids are really only tags of skin that are vascular and that become troublesome when inflamed. A great deal of anal itching is usually associated with hemorrhoids. Smith's (1943) report of three cases of lymphosarcoma resembling internal hemorrhoids, and the discussion that followed the presentation of his paper, caution against the making of snap diagnoses of "piles."

Diarrhea.—Early in all cases some attempt is usually made to control the diarrhea, though it is a fact that such success as rewards these efforts is nearly always only temporary. The following drugs are usually tried out in succession:

Bismuth subcarbonate, 20 to 30 grains (1.5–2 gm.) every three hours.
Bismuth betanaphthol, 10 grains (0.6 gm.) every four hours.
Calcium carbonate, 15 to 30 grains (1–2 gm.) every four hours.
Calcium glycerophosphate, 10 to 15 grains (0.6–1 gm.) every four hours
Acetyltannic acid (tannigen), 3 to 10 grains (0.2–0.6 gm.) every four hours.
Protan, 20 to 30 grains (1.3–2 gm.) every two hours.

Colic.—During the course of a severe attack, hot stupes applied to the abdomen, according to the method described under Pneumonia, often bring relief; morphine, 1/8 to 1/4 grain (8 to 15 mg.) or dilaudid 1/48 to 1/32 grain (1.3 to 2.0 mg.), or preferably codeine 1 grain (60 mg.), may be needed, of course paregoric in usual doses could also be used. Hurst gave tincture of belladonna (laudanum) every four to six hours, increasing from 5 minims (0 3 cc.) to the maximum amount that can be taken without uncomfortable dryness of the mouth resulting. He found a tablespoonful of charcoal several times daily also helpful. Bargen and Jackman (1939) found that the addition of 1/3 grain (20 mg.) of papaverine hydrochloride to an opiate-atropine mixture is helpful.

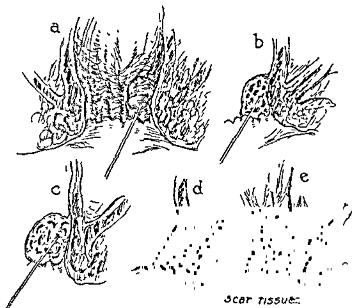
Local Applications.—Attempt is often made, by means of antiseptic enemas or topical applications, to bring about healing of the ulcers. It should be remembered that the tissues are highly sensitive to trauma in colitis, and overloading with excessively large retention enemas should therefore be avoided, and the soft catheter should be introduced only just beyond the anal sphincter. Eyerly and Breuhaus (1938) followed a cleansing enema in one hour with a retention enema consisting of 3 to 5 ounces (90–150 cc.) of 3 per cent aluminum hydroxide and 15 per cent kaolin in colloidal suspension mixed with an equal amount of sterile distilled water, the patient retaining this as long as there is no discomfort. Best (1936) used daily rectal injections of 2 to 4 ounces (60 to 120 cc) of cod liver oil.

Intestinal Oxygenation.—Felsen (1945) has for some years been studying the effects of altering the gaseous tension in the intestines by the rectal introduction of oxygen. Passage through warm water heats the gas, which is then allowed to enter through an ordinary soft rubber catheter introduced only a few inches; small divided doses are given three to seven times daily, the total daily dosage being 250 to 2000 cc. The patient may be in the upright posture, on the toilet seat, or in the recumbent position in bed. There is moderate distention of the bowel as far as the pylorus, but much of the gas is apparently rapidly absorbed since very little is ejected from the rectum Felsen believes that this treatment leads to the diminution of spore-bearing anaerobes, encourages the superficial growth of obligatory or facultative aerobes, and favors a homogeneity of intestinal flora; the effect of oxygen on [illegible] speculative.

[illegible] years ago reported [illegible] s. Early in 1947, Cantarow kindly informed me that the presently employed treatment consists in the giving of calcium lactate, 30 grains (2 gm.), or calcium gluconate, 60 grains (4 gm.), orally three or four times daily, three and a half to four hours after meals, the patient being cautioned not to eat between meals.

most men are nowadays employing: place the patient on the side in the Sims or a similar position and partially dilate the sphincter by inserting the finger before introducing a tubular anoscope of the Martin type. Usually 1 to 2 cc. of the sclerosing solution is injected through a long needle of small caliber, injecting one or two areas at a time and spacing injections about a week apart. The technic of employment of the solution is shown in the illustration below (reproduced through the courtesy of Dr. Neil W. Swinton, of the Lahey Clinic).

trant cases.



Technic of injecting hemorrhoids (Swinton, N W, Surg Clin. N A, 19, 669, 1939): a, the needle inserted into the internal hemorrhoid, well above the anocutaneous line and deeply into the hemorrhoid, b, a cross section showing the tip of the needle in a perivascular position, c, the distention of the internal hemorrhoid, d and e, the resultant scarification

Phenol—This agent seems to be greatly preferred in England and is also gaining favor in the United States Swinton (1939) wrote that after a comparative study he favored it. The usually employed preparation is 5 per cent phenol in almond, olive, or cottonseed oil; Yeomans (1942) preferred oil of sweet almonds because he felt that the animal oils are absorbed too quickly and that mineral oil is not absorbed but remains as a foreign body.

Alcohol—Alcohol seems to be preferred to anything else on the Continent,

THERAPY

Palliative Measures.—Prolapsed hemorrhoids are best sprayed with cold water, or a cold compress may be applied, in order to reduce the congestion; they may then be gently returned through the sphincteric canal by manipulation with the oiled fingers. Other palliative measures than this, I think, are no longer justified in view of the excellent results now to be attained by employment of either of the two curative measures; however, of the following prescriptions, the first is for an astringent rectal suppository, the effect of which can be modified by changing the proportion of tannic acid:

℞ Tannic acid	gr xv	1 0
Balsam of Peru	♏xxij	1.5
Bismuth subcarbonate	ℨiiss	10 0
Oil of theobroma (cacao butter)	ℨiv	16.0
Cerate	ℨss	2 0
Make 10 suppositories		
Label. 1 three times daily.		

And the second is for an analgesic suppository:

℞ Powdered opium	gr. vj	0 4
Extract of belladonna	gr. ij	0 12
Ethyl aminobenzoate.	gr. xviij	1 2
Oil of theobroma (cacao butter)	ℨij	12 0
Make 6 suppositories		
Label: 1 before bowel movement.		

For treatment of the itching see Pruritus Ani.

Surgery.—It is now urged by surgeons that internal hemorrhoids that are causing discomfort be removed by operation, a plea that is heartily endorsed by most nonsurgical practitioners since the operation is practically always successful, is not dangerous, does not incapacitate for a long period though the patient suffers much immediate postoperative pain, and oftentimes cures a stubborn constipation as well as the case of piles

Injection.—External hemorrhoids must never be injected. It is now the consensus that the injection treatment may be employed with fair hope of affording relief to patients whose internal hemorrhoids are small or medium-sized and not accompanied by infection, thrombi, pain, muscle spasm, or marked prolapse. Bleeding is nearly always stopped, but in many instances the relief obtained through injection is not permanent Turell (1947) said that about 65 per cent of a group of 100 patients personally treated and followed remained symptom-free during a follow-up period of observation ranging from thirty to thirty-six months; reinjection was required in over 30 per cent of the patients because of recurrence of hemorrhoids causing bleeding nine months or more following conclusion of the original course of treatments. He said that the complications most often reported upon are irreducible prolapse of the treated hemorrhoids into the anal canal, or abscess formation. It was his expressed opinion that suppuration in many cases is due to an unsuspected or latent inflammatory process that was either overlooked or impossible of correct diagnosis rather than to the injections *per se*.

ments are being given. Haskell's (1939) technic seems to be about that which

and at this point, with the passage of considerable amount of gas, the patient noted relief of the pain As the sigmoid was approached, normal mucosa came into vision. Subsequent examination a week later revealed a normal rectum. (h) There may possibly be a familial tendency; at least Hurst (1943) reported that the father and younger sister of one of his patients suffered from exactly similar attacks I expect that some day it will be suggested that these attacks may be bizarre epileptic equivalents.

THERAPY

There is really very little to describe for it is apparent that physicians, though well aware of the existence of this peculiar malady, have been treating it in the traditional fashion of the ostrich, both in themselves and in their patients. Perhaps now that it is brought out into the light and fully faced

air, I should think that this could be easily accomplished with the ordinary rubber bulb infants' enema syringe, usually at hand as a denizen of a dark corner in the bathroom medicine cabinet Ryle (1944) also described the experience of a colleague who obtained relief through distention of the rectum with water.

flexion

Allergic Factors.—It seems to me that it has taken the allergists a long time to learn that Thaysen has raised this condition to a position of respectability since there would seem a fair chance that they might reasonably claim it for their own Several years ago Bramigk (1935) obtained relief in two cases by use of Rowe's elimination diets

Tobacco.—Several years ago I recorded a case in which, arguing the analogy between these attacks and those in "pseudo" angina pectoris, the patient was required to stop smoking with resultant complete relief Ryle (1939) seems to investigate the smoking habits of his patients, but records only one instance in which the patient stopped smoking, other adjustments were made in this patient's life at the time, but it is noteworthy that the attacks ceased to occur However, proctalgia fugax also occurs in nonsmokers.

Amyl Nitrite.—Marshall's (1935) patient obtained as certain, quick and complete relief from amyl nitrite as does the angina sufferer "A few seconds with a capsule and a handkerchief at the side of the tennis court, or in the

a state of premenstrual tension and had had a very fatiguing day

PROCTALGIA FUGAX

(*Spasmodic High Rectal Pain*)

Shortly before his untimely death, in 1936, Dr. Th. E. Hess Thaysen, of Copenhagen, recorded a series of cases of fleeting, but severe rectal pain unassociated with other signs or symptoms, to which, with due apology for the philologic heresy of coupling a Latin adjective with a Greek substantive, he gave the name "proctalgia fugax." The flood of communications "to the editor" which followed the appearance of his paper, together with many conversations among physicians, have amply confirmed not only the existence but the frequent occurrence of this entity. The sufferers are usually adults and apparently more often males than females; there is no associated rectal or anal pathology, nor is there any evidence that the malady affects or is affected by intercurrent diseases, or that it shortens the duration of life. The victims merely suffer at varying intervals, oftentimes through a long series of years, fleeting attacks of excruciatingly severe pain whose site is practically always indicated to be within the rectum just above the anal sphincter. In his Croonian lectures on the visceral neuroses, in 1939, Ryle included mention of fifteen cases of proctalgia fugax, and Lauda, in Vienna, reported a group of cases in the same year (not knowing, in fact, that the entity has been previ-

[illegible] ases of high rectal

[illegible] ort; it seems that

[illegible] 17. *Characteristic*

[illegible] with a sensation

of pressure high up in the rectum lasting a few moments, the pain develops rapidly to quite agonizing proportions, and then recedes slowly during several minutes; the average total duration is ten to fifteen minutes although attacks not infrequently last longer and now and then seem to be aborted before reaching full force. (b) The patient may gasp for breath and experience some degree of substernal tightness but these manifestations seem to be not the

[illegible] ting, pallor, and momentary loss of con-

[illegible] 'iates and the attack is neither preceded,

[illegible] disturbances of intestinal function (dis-

tention, tenesmus, constipation, or diarrhea). (d) An attack begins unaccountably at any time of day or night and seems to be unrelated to the state of rest or activity in which the patient finds himself at the moment. (e) Association with coitus, masturbation, migraine and epilepsy has been reported, but certainly in the majority of cases no such relationship has been established (f) In the few recorded instances in which physicians have made digital examination of themselves during attacks, anal spasm has not been observed, and it has been noted by numerous patients that the stool may be passed with accustomed ease during an attack, though it is said that after defecation the pain sometimes seems to be accentuated in degree and extended in duration. (g) Bolen (1943) had the good fortune to be able to examine a patient sigmoidoscopically during an attack. He found the rectal mucosa redder than normal, seemingly swollen, and the vessels prominent. The site of the pain was at the central portion of the levator ani muscle and slight

[illegible] caused mild spasm

[illegible] per-

[illegible] idal

[illegible] wel,

INFECTIOUS HEPATITIS

(See *Infectious Hepatitis* among the *Infectious Diseases*)

HOMOLOGOUS SERUM JAUNDICE

(See *Infectious Hepatitis* and *Homologous Serum Jaundice* among the *Infectious Diseases*)

THE CIRRHOSES

The study of the cirrhoses of the liver has only recently been taken up

to be quite wide of the truth, for much has been learned in recent years "The subject is ripe for investigation," says Rowntree; "it awaits the touch of a Richard Bright" But, pending the arrival of the new Bright, I must content myself with a more or less conventional listing of the entities

The cirrhoses, then, may be divided into (a) portal, (b) syphilitic, (c)

applies also to Banti's disease, Wilson's disease and hemochromatosis, in all of which cirrhosis forms a part of the picture). The syphilitic affections

mother. "Cardiac" cirrhosis is the term applied to describe the state of diffuse

given in the section below

PORTAL CIRRHOSIS

The clinical entity recognized as portal cirrhosis results from prolonged inflammatory, degenerative, or proliferative changes in the liver, which are believed to occur in the following sequence: (a) degeneration of cells in the periphery of the lobules, (b) proliferation and contraction of interstitial tissue

DISEASES OF THE LIVER AND BILE PASSAGES

JAUNDICE

the other anemias, familial nonhemolytic jaundice and Weil's infectious jaundice are to be ruled out. In lobar pneumonia, jaundice is probably always

in relapsing fever,

is, and it is often

chemical poisons

may cause toxic hepatitis and jaundice: arsenic, antimony, acetic acid, carbon tetrachloride, cinchophen, chloroform, dinitrophenol, phenylhydrazine, potassium chlorate, phosphorus, picric acid, snake venom, mushroom poison, trinitrobenzene, tetrachlorethane, trinitrotoluol. Jaundice may appear in eclampsia and following accidental or operative trauma; it may arise from any one of a number of mechanisms in chronic heart disease (its sudden appearance *in myocardial insufficiency points toward pulmonary infarction); and it is one* of the symptoms following the transfusion of incompatible blood.

and Crawford (1944)

oms in-

ordinary

icterus neonatorum is physiologic, being a reflection of the presence in the blood of an increased amount of bilirubin resulting from hemolytic destruction of surplus erythrocytes, the etiology of the rare and fatal Winckel's disease is still unknown, icterus gravis neonatorum (erythroblastosis fetalis) has been the subject of a great deal of study in recent times and the significance of Rh negativity in the blood of the mother and Rh positivity in the blood of the

aken

Con-

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there in-

dice" a-

ately described as "infectious hepatitis", under the he

entity is discussed in the section on Infectious Diseases, where there is coupled with it a discussion of the nearly related homologous serum jaundice

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BLEEDING IN OBSTRUCTIVE JAUNDICE

(*See Vitamin K Deficiency*)

cases such symptoms of hepatic insufficiency as malaise, nausea and vomitin headache, depression, loss of memory, and delirium or coma may be seen. T majority of patients do not die from hepatic insufficiency directly but fro the complicating disorders, such as circulatory failure, hemorrhage, ascites and intercurrent infectious disease, particularly pneumonia or a rapid tuberculosis

John Brown described a case of cirrhosis in 1685, John Andre in 1788, and Matthew Baillie in 1818, both wrote on the subject, but the first adequate account was that of Laënnec, who gave the disease its name in 1819.

THERAPY

Diet and Vitamins.—The production of cirrhosis in experimental animals by dietary alterations is now accepted fact but of course such deliberate studies cannot be performed in the human, nevertheless there is now ample pragmatic evidence that in man at least amelioration of symptoms can be effected by the institution of dietary measures Numerous observers have reported good results with a new diet, but I shall report here the methods and results obtained by Patek (1943), with whom this work began a number of years ago. The new diet constitutes a marked departure from the high carbohydrate and low protein and fat diet that had been so long used in treatment of the disease, since it comprises a diet very rich in protein and ample in both carbohydrates and fats Patek's diet contains 3591 calories in the following proportions: protein 139 gm (including the protein in brewers' yeast), fat 175 gm, carbohydrate 365 gm It employs principally meat, milk, eggs, fruit and green vegetables Meat is served twice daily, milk five times daily—three times with meals and two times with 25 gm of powdered brewers' yeast It is usually found advisable to feed the yeast in graded increasing doses up to the final amount; for the occasional patient who cannot tolerate brewers' yeast, oral vitamin B complex must be substituted in the form of liquid yeast concentrates In addition, thiamine chloride (5 mg) is injected intramuscularly daily and liver extract (5 cc) twice weekly All who use these diets remark that the task of getting this much food into the patient is very difficult because the individual with cirrhosis often finds food loathsome The diet chart of Patek and Post, altered by the omission of a semiliquid diet which they also included for use in exceptional cases, is presented in Table 21 The reader will find charts of food values in the article on Diabetes

Patek's experience, since amplified by him and confirmed by others, is the following two months were required on the average before definite improvement became apparent, but at the end of the first year the survival rate was 57 per cent in a group in which this treatment was given as compared to 39 per cent in the group treated by older methods, at the end of the second year 45 per cent of the patients had survived as compared to 21 per cent who were not treated in this new way

More recent modifications of the high protein diet of the general type of Patek's comprise the raising of the protein fraction and the lowering of the fat. Kimball *et al* (1947) said that the mortality in their eighty-six patients treated on a high protein-high vitamin-low fat diet was one-fourth less and the survival time two to four times greater than that of the fifty-seven patients not so treated, their patients received 150 to 250 gm. of protein, 350 gm. of carbohydrate, and only 60 gm. of fat.

size, but it may be enlarged and smooth due to the deposition of fat. The spleen is also frequently enlarged, whether merely by reason of venous congestion or because the liver is not an isolated organ but exists as part of a "splenohepatic" system, is not known. Boles *et al.* (1947) take the position that alcohol as well as chronic infection, toxemia, disturbances of metabolism, tissue susceptibility and no doubt central nervous system influences all play their role in the causation of portal cirrhosis, and that in the light of our present knowledge the disease might well be regarded as not essentially due to alcohol or any other known specific factor. They point out that in the great majority of alcoholic addicts, so far as is known, cirrhosis does not develop, though doubtless alcohol is much to blame in certain individuals. The studies of Patek and others in recent years are certainly pointing toward definite vitamin A and B-complex deficiencies in so-called alcoholic cases It has been alleged that beer is less prone to cause cirrhosis than wines and "hard" liquors. However, cirrhosis does also undoubtedly occur among nondrinkers, not only alleged nondrinkers

Eastern peoples.

Portal cirrhosis occurs most frequently in the early forties and terminates fatally in the early fifties Men are more frequently affected than women in about the proportion of 2 or 3 to 1. In their very thorough analysis of 386 cases, Ratnoff and Patek (1943) found an increased incidence in patients of Italian and Irish stock but no convincing evidence of hereditary predisposition; Karsner's (1943) study indicated that Negroes are somewhat more susceptible than whites. The early symptoms are dyspeptic and are rarely recognized, though the new tests of hepatic function should make diagnosis easier now than it was a few years ago; parenthetically, however, one should note that Watson (1944) and his associates at the University of Minnesota, who are studying this matter intensively, believe that the concomitant employment of several types of test is necessary in order to obtain information of value. In a fully established case the patient has lost much weight and energy, has a muddy complexion, sunken eyes and a sharp nose on which there are distended venules; he complains of dyspepsia and perhaps of hemorrhoids and of an intensely itching skin. Engorgement of the veins in the abdominal wall and elsewhere is a striking evidence of the attempt that is being made to establish a collateral circulation Ascites occurs in more than 50 per cent of cases, the abdomen sometimes containing as much as 15 liters of fluid. Both the spleen and the liver may be found to be enlarged. The urine is usually scant and highly colored; in some cases there is a pernicious-like anemia. Purpura and a tendency to easy bleeding are very common, and profuse hemorrhage from the stomach, due to the anastomoses formed about the lower end of the esophagus, is a frequent and serious occurrence. The statistical study of Ratnoff and Patek (1942) indicated that in addition ... ominous prognostic ... with the ... advanced

Broun and Muether (1942), and Russakoff and Blumberg (1944), have

Labby *et al* (1947) believed that the employment intravenously of large doses of crude liver extract two or three times weekly was of value in restoring and sustaining appetite in previously anorexic patients; they felt that when used in conjunction with a full diet this intravenous liver therapy effected a

carbohydrates No dietary supplements of vitamin or other nature were employed In many of the patients under this new type of therapy, ascites, peripheral edema and other manifestations of the disease disappeared, liver function tests indicated an improvement during the treatment period, and there was evidence at the time of the report of an increase in the survival period in the group of thirty patients studied The special liver extract employed was prepared at the Rockefeller Institute and is not as yet available for general use Morrison (1947) has evolved a method of therapy in which he employs

Replenishment of Blood and Proteins.—Transfusion is often resorted to in cirrhosis not only for its temporary restoration of erythrocytes but also be-

the hope that the overgrowth of connective tissue might thus be corrected, but I do not know that the survival of this practice rests upon any more secure footing than the rather vague clinical impression that it is of some value It is of course an extremely difficult matter to put to the test of controlled clinical experimentation

Focal Infection.—It is generally agreed that all demonstrable foci of infections should be eradicated if this can be accomplished consistently with the safety of the patient; that such treatment serves to arrest the progress of the disease can rarely, if ever, be shown, for whatever contribution the infectious process may have made toward the establishment of the disease has become accomplished fact long before the diagnosis of cirrhosis is made.

TABLE 21.—CIRRHOSIS DIET (AFTER PATEK AND POST)

	Amount	Proteins	Fats	Carbohydrates
Breakfast				
Fruit 18%	1 serving			18
Cooked cereal or	200 grams	4	2	20
Prepared cereal	30 grams			
Sugar on cereal	12 grams			12
Eggs. . .	2 only	13	10	
Milk. .	200 cc.	6	8	10
Toast.	60 grams	4	1	30
Butter.	20 grams		17	
Coffee				
Cream 20%	30 cc.	1	6	1
Sugar. . . .	12 grams			12
9 A.M. Brewers' yeast	25 grams	12.5	0.5	8.5
Milk.	150 cc.	4.5	6	7.5
Sugar	12 grams			12
Dinner				
Meat, medium fat.	100 grams	17	20	
Vegetables 5%.	100 grams	1		4
Vegetables 10%	100 grams	2		9
Vegetables 20%	100 grams	3		19
Bread.	30 grams	2		15
Butter. .	20 grams		17	
Dessert (cake, pudding)	1 serving	5	8	25
Milk . .	200 cc	6	8	10
Coffee				
Cream 20%.	30 cc	1	6	1
Sugar	12 grams			12
2 P.M. Brewers' yeast	25 grams	12.5	0.5	8.5
Milk. . .	150 cc	4.5	6	7.5
Sugar	12 grams			12
3 P.M. Orange juice	200 cc			18
Supper				
Soup (Julienne) .	200 cc	4		4
Meat, medium fat	100 grams	17	20	
Vegetables, 5% salad	100 grams	1		4
Vegetables, 20%	100 grams	3		19
Bread	30 grams	2		15
Butter. .	*20 grams*		17	
Milk	200 cc	6	8	*10*
Fruit 18%.	100 grams			18
Tea				
Cream 20%	30 cc	1	6	1
Sugar .	12 grams			12
7 P.M. Milk	200 cc	6	8	10
Grand total.		139	175	365
	Calories 3591			

as promoting the development of collateral circulation by giving external *support to the splanchnic circulation*; but there is no doubt that too long delay of tapping is inadvisable. Some external abdominal compression should be used after paracentesis to prevent as far as possible rapid distention of the portal tributaries and reaccumulation of effusion The operation should be performed as frequently as the reappearance of ascites, in considerable amount, requires."

Diuretics.—For discussion of the drugs, see Congestive Heart Failure. By general consent the best of them in cirrhosis are the mercurials, but the best is none too good It is notable that Butt and Snell (1942) said that at the Mayo Clinic in recent years treatment devoted principally to the elimination of ascites by mercurial diuretics, restriction of fluids and purgation, has been largely abandoned in favor of the type of dietetic approach described above.

Surgical Treatment.—A number of short-circuiting operations to divert blood from the collateral circulation, as well as measures to establish additional connections between the portal and the general circulations, have been employed with variable results The best known of these, the Talma-Morison omentopexy, certainly does not have a brilliant record. Cates (1943) reported that 42 per cent of the thirty-eight patients operated upon in his series died [illegible]

almost exclusively as a last resort but were done earlier in the disease in more [illegible]

of patients who seemed otherwise doomed. Splenectomy, though giving great relief in some cases by removing a substantial burden from the portal circulation, is also accompanied by high surgical risk and not generally productive of excellent results

Hepatic Insufficiency.—In advanced cases in which there is a very great depression of liver function, such symptoms appear as loss of memory, delirium, convulsions and coma. These manifestations of toxemia may usually be made to disappear, at least temporarily, under the administration of adequate amounts of water and carbohydrate. It has now become the almost universal practice in these cases to administer 5 to 10 per cent dextrose solution intravenously either in amounts of 1 to 3 liters during the day or steadily by the continuous drip (venoclysis) method. The question of the advisability of employing insulin in addition seems to me to have been settled in the negative by Soskin and Hyman (1939), who pointed out that in a non-diabetic patient under these circumstances the administration of insulin pro- [illegible]

Dyspepsia.—In the beginning of the chapter on the Gastro-intestinal Diseases are discussed measures for the treatment of dyspepsia; they nearly always fail when instituted for the control of the dyspepsia accompanying cirrhosis of the liver, the reason being that such dyspepsias are due to congestion throughout the gastro-intestinal tract and that they are relieved only when the congestion is made to decrease, *i.e.*, when the cirrhotic process is abated or arrested.

Itching.—Sponging, not rubbing, with a hot solution of sodium bicarbonate followed by dusting with talcum powder, or the application of 1 per cent menthol in alcohol, or an ointment of 1 per cent phenol, may be tried. One of the calamine lotions, or the oatmeal bath (see in Eczema), is helpful to some individuals. Sometimes sweating brings relief, either induced by applied heat or the use of pilocarpine nitrate 1/10 to 1/5 grain (6 to 12 mg.) by mouth or hypodermically, repeated so as to maintain mild diaphoresis; in some individuals aspirin (acetylsalicylic acid) will produce as much sweating with fewer side actions. Lichtman reported, in 1936, that since his introduction in 1931 of the use of ergotamine tartrate in cases of intractable itching, he had obtained relief in about half his seventy-five cases; numerous other observers have also used the drug with satisfaction: ergotamine tartrate 1/60 grain (1 mg.), three times daily by mouth, or subcutaneously or intramuscularly once a day in a dose of 1/60 to 1/20 grain (1–3 mg.). But one must not overlook the potential toxicity of this drug; see under Migraine. Prinzmetal (1934) used the nitrites with satisfaction, giving amyl nitrite, nitroglycerin, or erythrol tetranitrate just as in angina pectoris In the experience of Rowntree and many others,

given intravenously in a dose of 7½ to 15 grains (0.5–1 gm.), to be repeated as necessary. Insulin in small dosage, without accompanying dextrose, has been said to be helpful in a few cases; calcium salts may also be worth trying Wilbur (1947) pointed out that in occasional instances, when all other measures have failed or are contraindicated, the intravenous injection of procaine hydrochloride may give striking relief in dosage of 20 cc. of the 0.1 per cent solution (1 gm in 1000 cc of isotonic saline) given intravenously very slowly. Relief may be quite dramatic and may last for two to four hours or more

Hematemesis.—Attempt should be made to maintain a normal prothrombin

approached by ligation of the coronary veins of the stomach or resort to the other surgical procedures mentioned later; the varices have also been successfully treated through the use of sclerosing injections.

Ascites.—*Paracentesis*—Soon or late all cases have to be tapped. The tapping is a procedure which it were idle to attempt to describe here since its technic can only be learned in the clinic. The indications, however, are another matter; they are well stated by Kern

"Tapping should not be delayed so long that serious displacement of the diaphragm and excessive intra-abdominal tension have occurred. Something might perhaps be said in favor of the possible usefulness of moderate effusions

erosions of the mucous membrane. Gallstone colic is due to spasm of the inflamed muscular viscus, to its distention with bile, to the temporary lodgment of a stone in the cystic, hepatic, or common duct, or to spasm of the sphincter

center for what he calls "poisoned bile," through its lymphatic connections with the liver and pancreas, but that hepatitis and cholangitis also play a prominent part in the pathologic picture; his position is that the liver, the gallbladder and the ducts are guilty of initiating a vicious circle since they pour into the duodenum "poisoned bile" which, being taken up by the mesenteric veins and lacteals, is conveyed throughout the body "to exert a harmful effect on all tissues" I do not believe that he has proved the "poisonous"

Gallstones were first recorded by Gentile da Foligno in the fourteenth century.

THERAPY

Dietetics, Nonsurgical Drainage and General Treatment.—It seems to me that about all there is to the *dietetics* of chronic gallbladder disease may be simply stated (a) Nobody having ever conclusively shown in the human that substances high in cholesterol content (brains, sweetbreads, kidneys, liver, fish roe, egg yolk are the principal ones) are really conducive to gallstone formation, there is really no reason for eliminating these substances from the diet (b) Fats make some of the patients uncomfortable probably by increasing cholecystokinin production and thus promoting gallbladder

England, was well known as a stout champion of the use of the drug: the patient takes the largest dose short of that found upon experiment to cause

1922, and Soper since 1925, both reporting good results, the former also has some fat taken thirty minutes after the salt in order to contract the gallbladder Lyon prefers to introduce the duodenal tube and, when its tip is in the correct location, to introduce 40 to 50 cc of 33 per cent magnesium sulfate solution. In a little while, bile begins to flow out of the tube; at first it is light lemon-colored (A bile), then it changes to a more viscid consistency and is golden brown or green (B bile); and then it changes again and becomes much lighter and thinner than either of the two previous specimens (C bile)

CHRONIC GALLBLADDER DISEASE

Although chronic cholecystitis and cholelithiasis are possibly *separate* entities, they are nevertheless so similar in their symptoms and in the therapeutic measures with which we attempt to control them that it is legitimate and convenient to discuss the two conditions here under the common title of "chronic gallbladder disease." The victims of this disease are more often women than men and are usually near or past their fortieth year "Female, fair, fat and forty" used to be a diagnostic alliteration of my student days —but not a very accurate one, I am convinced, for many persons who are described by none of these terms do have the disease. The symptoms are those of dyspepsia, such as acid eructations, nausea, flatulence, heartburn, and especially chilliness and a feeling of weight in the abdomen after eating During acute exacerbations there is pain and tenderness in the gallbladder region, chilliness, malaise, more or less precordial oppression and perhaps a slight bit of fever There are usually frequent asymptomatic periods A typical attack of gallstone colic—which is an acute condition not to be confused with the chronic state just described—occurs almost invariably *in the middle of the night; the patient experiences excruciating pain in the* upper right quadrant of the abdomen, which radiates all over the abdomen and into the back, the shoulders and even down the arms; she sweats profusely, is usually much excited and assumes many different positions, both in and out of bed, in an attempt to put an end to the agonizing pain Such an attack usually persists only a few hours, but it may last for several days with remissions. When palpation becomes possible, on the subsidence of pain, it will be found that the gallbladder region is exquisitely tender; usually some degree of jaundice appears also after the paroxysm is over, or at least the urine will be bile-tinged and the feces undercolored Chronic obstructive jaundice is rare in gallbladder disease unless there is an accompanying chronic cholangitis of considerable degree It is to be noted that colic may occur in cases of chronic gallbladder disease in which there are no gallstones present, it is assumed that in these instances a motor type of dysfunction occurs to which the name "biliary dyskinesia" is applied It is furthermore now well established (Rosenthal, 1944) that gallbladder disease and particularly gallstones are frequently encountered in the autopsies of elderly patients [illegible] lelithiasis [illegible] f the gall- [illegible] the bile; as yet we have very little exact information on the subject. Jones (1945) has presented the interesting viewpoint that the formation of gallstones may be a normal process the mechanism of which is continually operating, and that the [illegible]

composition of the bile, the formation of stones is accelerated. Jones feels that during life the calculi may form and redissolve as conditions vary in the flow of the bile. In chronic gallbladder disease, either with or without gallstones, the pathology in and about the gallbladder varies greatly; there may be a simple catarrhal inflammation with moderate swelling of the mucous membrane; or the viscus may be distended with mucopurulent material; or there may be many adhesions binding it in a distorted shape to the liver, pylorus and duodenum; or it may be much thickened and contracted and show actual

by reason of the really
in many people when

enema of warm physi-
will often bring relief;

men prefer pantopon in dosage of 1/3 to 1/2 grain (20-30 mg.) by mouth or hypodermically. Batterman (1943) employed the new synthetic analgesic drug, demerol, with satisfaction in biliary colic; the drug, which has been shown to be addictive like the opiates, is usually employed in a dose of 5/6 to 1½ grains (50–100 mg.). It is customary to employ atropine with the opiates, but Walters *et al.* (1937) did not find that this drug even in large

the method is still in use and productive of good results provided there is not too much associated inflammatory disease at the time of the attack. Beware, proceed calmly here, even though the patient is writhing in pain; see Lead Poisoning for the reasons. In a small series of cases, McGowan *et al* (1936) obtained relief through the use of nitrites as in angina pectoris; Walters *et al* (1937), Best and Hicken (1938), Vohn and O'Brien (1939) and McGowan and Henderson (1940) also reported satisfaction with these drugs in small series of cases in which sphincter spasm appeared to be the cause of the pain. Gladstone and Goodman (1941) injected 0.25 to 0.5 gm. of aminophylline and obtained satisfactory relief of pain in their small series of cases; the drug was given intravenously and with no bad effects but the authors warned that the injection must be made very slowly In rare cases, light or even relatively deep general anesthesia must be instituted in order to bring release from the agony Return to full diet after the attacks must be very gradual

Surgery.—Medical measures, though they will carry a patient through an attack of colic, will not cure gallstones, that is to say, we know of nothing that will effect the dissolution of the stones, and so long as they remain these attacks are likely to recur in those subject to them There does not

light of the shortage of hospital beds in War II, concluded that operations may be safely deferred in patients with gallstones so long as there is no evidence of complications and provided postponement is not so protracted that it may impair the patient's resistance to the operative procedure. Indeed, many medical men feel there is no evidence that delay occasions any serious threat to the welfare of the patient whose colic has been mild, and that recurrence may not take place for a very long time. However, when a stone has become impacted in the common duct, or when the attacks are frequent

The A bile is said to come from the common bile duct, B from the gallbladder, and C from the liver itself (*i.e*, freshly secreted bile) but there is very little proved fact to support these assumptions. Lyon cites many cases in which improvement in symptoms has followed upon single or repeated drainages with the duodenal tube, but study of his book and his subsequent publications leaves some of us rather skeptical. The enthusiasm of himself and his followers is at times almost hilarious, but they claim results in almost all the ailments to which man is heir, and they certainly do not show that the mental attitude of their patients is not tremendously affected by the atmosphere of almost religious awe with which the institution of a "drain" has come to be surrounded. Collins (1940) stressed the point, in behalf of tube drainage, that hypertonic magnesium sulfate solution given by mouth is reduced to isotonicity and that a part of the solution is converted in the duodenum into sodium sulfate which is thought perhaps to constrict instead of relax the sphincter of Oddi—however, by no means all of the magnesium sulfate is so converted and it is not proved that sufficient does not survive to promote the "drainage" even though the ritual of the tube has not been performed. As to the possibly harmful effects of having infected bile pass out through the intestine instead of through the tube, witness Carlson: "We are swallowing bacteria every day. There are a few bacteria that are specifically toxic in the intestine. There are a few toxins poisonous by mouth, but, so far as I know, we could eat pus, ordinary pus and not be influenced, excepting esthetically. It is not clear, therefore, that finding bacteria or pus in the duodenal content means injurious effects from the bacteria or bile lower down." It seems to me that the only significant difference between the peroral and the tube methods of "nonsurgical biliary tract drainage" is that in one the bile goes down and in the other it comes up; in either case it goes out. The Lyon type of tube drainage is being performed less and less as a therapeutic measure as the years go by

Bile salts, perhaps best given in the form of decholin, 4 to 8 grains (0 25 to 0.5 gm) two or three times daily, stimulate the production of bile; but since no one has proved that in gallbladder disease the liver usually fails to secrete properly, I cannot understand the rationale of the routine employment of bile salts. Ivy and Berman (1939) seemed to look upon the two chief indications as: (a) to "flush" the biliary passages with a copious flow of bile of low viscosity in the hope of counteracting a tendency toward stasis, (b) instances in which there is sufficient hepatitis to diminish bile salt synthesis but not to prevent bile pigment excretion, *i.e.*, bile salt deficiency in the presence of pigmented feces. The evidence for the very frequent occurrence of either of these indications is not clear to me in the literature. However, bile salts are very plentifully employed in practice; therefore I must be wrong

From the investigations of Zaslow *et al.* (1947) it appears that the major factor concerned in the presence of *penicillin* or *streptomycin* in the bile of the gallbladder is the patency of the cystic duct, for these agents apparently do not get into the lumen of the gallbladder through blood vessels in the wall of the organ. This observation is a significant one since it is said that in most cases of acute cholecystitis and empyema there is also present obstruction of the cystic duct.

Spa treatment is often of value in cases of chronic gallbladder disease, not so much because of the mineral content of the waters as because of the fact

DISEASES OF THE RESPIRATORY TRACT

CHRONIC BRONCHITIS AND EMPHYSEMA

Sydenstricker, of the United States Public Health Service, has pointed out that the use of death rates as an index of the prevalence of disease has become so universal that the problems and aims of public health are set forth almost entirely in lethal terms when statistics are used. Valuable statistics these, but their use unfortunately sometimes serves to obscure the fact that there is still a tremendous amount of "ill health" in the world, even though people so fortunate as to dwell in civilized lands do not die so young as they did a few decades ago. What doctor of any experience at all needs to be told that the ailments of most individuals are seldom dangerously severe, though they are nevertheless of very great importance both to the individual and the community? Among these important affections that make people simply "sick," acute and chronic bronchitis and emphysema

the *most* important place, for it is certain that an upper respiratory infection is the diagnosis most often made in home visits in Great Britain and the United States—doubtless this is also the case in the other North Temperate countries as well. The winter cough, often becoming a year-round cough, of late middle-aged and elderly people, coupled with shortness of breath and cyanosis on exertion, *i.e.*, that which we call chronic bronchitis and emphysema, *may* be just that, but the wise practitioner makes a careful search for a possible underlying cardiovascular disease, aortic aneurysm, bronchiectasis, asthma, gout, syphilis, or some other debilitating disease.

THERAPY

The treatment of chronic bronchitis and emphysema has advanced hardly at all since the days of our great-great-grandfathers Moderation in all things, a quiet and regular life with shunning of all vigorous pursuits, a residence in the South during the winter—all of these measures are quite helpful to the few for whom they are possible. It would seem that the sojourn in the South had best not be in a region of excessive dampness; Cohen (1944) found many cases of chronic bronchitis much exaggerated in individuals who had come to Panama and he ascribed this chiefly to the dampness of that region. The treatment of cough is described under Common Cold. Both Wilson and Findley (1944), and Christie (1944), said that ephedrine will bring relief to a considerable number of these patients; the former authors offered the following prescription in which the effects of ephedrine are obtained together with the relaxing action of belladonna and the expectorant action of the iodide:

℞	Ephedrine sulfate	gr. xv	1 0
	Tincture of belladonna	ʒi	30 0
	Potassium iodide	ʒi	30 0
	Syrup of cherry	℥iv	120 0
	Water to make	℥viij	240 0

Label Teaspoonful every 4 hours.

and the general health fai
indicated. Alvarez (1944)
those persons with a bad
out-of-the-way places where a good surgeon is not available. Common duct operations are the most dangerous—a fact upon which many surgeons base their plea for operation in any case in which gallstones have been diagnosed with certainty, since this will in most instances save the patient the risk of a possible operation for stone impacted in the duct. Miller's (1932) study of the association of cardiac pain with disease of the gallbladder has caused a number of surgeons to recall instances in which "heart trouble" disappeared after cholecystectomy.

The problem of the persistence of "biliary dyskinesia" after operation for presumed cholecystic disease is well known to all and most perplexing to the surgeons. Recently, Gray and Sharpe (1944), of the Mayo Clinic, said that in cases in which pain persists or recurs after cholecystectomy, and in which reoperation is deemed necessary, diligent search should be made for a suspected remnant of the cystic duct, whether or not calculi are suspected in the common bile duct; they also laid great stress upon the importance of operating

edochal sphincterotomy in a small series of cases.

being 13.5 years Kay *et al.* (1947) said that death usually results from pneu-

pointed out that there is a type of myocarditis that occurs in patients with

often very difficult and usually rests finally upon the injection of iodized oil into the bronchial tree with subsequent roentgen study.

THERAPY

Lobectomy.—The technic of this operation has improved so much that many thoracic surgeons are now hopeful of some day being able to offer complete relief in this way to practically all patients Diamond and Van Loon (1942), in making a plea for operation on all patients as young and as early as possible, pointed out that as a rule children tolerate lobectomy better than adults and that in them there is a far better compensation for the loss of the excised areas Kay *et al* (1947) recorded the performance at one of the general hospitals during War II of 220 consecutive lobectomies with only one death. However, Olsen (1946) pointed out that in many instances study of pulmonary function discloses that the patient's respiratory reserve is not sufficient to permit operative interference, in a large group of patients the process is so extensive and wide-spread that the removal of a single lobe would not be of help He felt also that in bronchiectasis accompanying asthma or asthmatic bronchitis resection is seldom indicated.

General Medical Treatment.—The general hygienic treatment of tuberculosis is profitably employed in advanced cases of bronchiectasis; *i e*, the patient should rest a great deal, if not entirely confined to bed, and should be given a well-balanced nutritious diet and as much spiritual encouragement as possible.

Postural Drainage.—Patients do not have to be encouraged to employ this measure for they have often found the most suitable posture for drainage of their own accord King (1939) said that with lower lobe involvement the best position is on the face with the shoulders lower than the hips; some patients lie across the bed with the shoulders near the floor, others kneel in a chair with the hands on the floor Alexander (1944) remarked that the taking of a half dozen deep breaths before each half dozen hard coughs loosens the secretions better for expectoration and aerates the affected portion of the lung better than if the inversion and coughing are alone relied upon. Lying on the back with the foot of the bed moderately elevated seems to serve best in

is lying on the uninfected side In some hospitals postural drainage beds are available nowadays.

Chemotherapy.—*Penicillin* —It seems apparent that aerosolized penicillin, with perhaps aerosolized streptomycin in combination with it in selected cases, is finding its greatest usefulness in the preparation of patients

Some patients are relieved by the performance of exercises designed to improve the *expiration*, while others are helped by the wearing of a special type of abdominal binder. Inhalation of oxygen or oxygen and helium mixtures sometimes temporarily relieves the difficulty in respiration but of course these agents are seldom available to this type of patient who is not in hospital. Southwell (1946) reported the employment of penicillin by inhala-

[illegible]

reported considerable improvement in fifteen of their twenty cases of chronic bronchitis treated by penicillin inhalation.

BRONCHIECTASIS

Increasingly in recent years the profession has become aware of the large number of cases of bronchiectasis occurring independently of any association with pulmonary tuberculosis, pneumoconiosis, or tumor of the lung; indeed, one finds some qualified observers who feel that the condition is about as common as tuberculosis. Case distribution is about equal at all ages, but

[illegible]

chronically ill in appearance, is dyspneic on exertion, has clubbed fingers, has fever at intervals, coughs a great deal and usually but not invariably expectorates a great deal; the sputum is often but not always very foul, and often but not always it stratifies into three layers on standing. Pulmonary hemorrhages are of frequent occurrence. It is generally considered that the classification of the dilatations into the cylindrical, saccular and varicose [illegible] classifications, such [illegible] or pres- [illegible] le lobe, the whole of one lobe, or part or all of many lobes; but apparently after it is once established it seldom spreads from one lobe to another. But infection may spread from the bronchial walls to involve the peribronchial and pulmonary tissues, giving rise to suppuration and foul sputum. With regard to etiology the consensus is that the condition is a sequel of pulmonary infections such as pneumonia, empyema, abscess, tracheo-bronchitis, or influenza, or of chronic sinus disease; Rilance and Gerstl (1943) felt that bronchiectasis secondary to tuberculosis is in most instances merely a benign bronchial dilatation not associated with abnormality of bronchial function. *Watson and Kibler (1938) believe that there is a definite* chain of events in most cases: first, an allergic bronchitis; second, atelectasis; and finally, bronchiectasis. Olsen (1946) said that their impression at the Mayo Clinic is that the allergic diseases are not primary factors in the etiology of most cases; he had earlier expressed the opinion that both congenital and acquired components enter into the production of the disease. The only extensive prognostic study I have seen in which no case that had not been followed for at least five years was included is that of Bradshaw *et al.* (1941): 34.5 per cent of their 171 patients died of bronchiectasis or its complications, the average duration of life in the dead patients from the onset of symptoms

Collapse Therapy.—It is the consensus that these measures, so useful in pulmonary tuberculosis, are seldom helpful in bronchiectasis and that their employment may preclude subsequent lobectomy.

X-Ray Therapy.—Berck and Harris (1937), at Mount Sinai Hospital in New York, treated a small group of chronic cases with moderately large doses of roentgen ray with a considerable degree of improvement in a fair proportion of the cases Fink (1941) said that they concluded at the University of Minnesota Hospitals that little was gained by roentgen therapy usually, though it might be worth trying in selected cases.

[illegible]

overcome the foul odor, in some such prescriptions as the following:

℞ Creosote (beechwood)	gtt vj	0 4
Glycerin	℥j	32 0
Peppermint water (or plain water) to make	℥iij	96 0
Label Two teaspoonfuls every two to four hours, well diluted		

This prescription contains a small amount of the drug, but when it is finished the next should contain double this quantity—*i e*, 12 drops The creosote should then gradually be increased to the point of tolerance as marked by anorexia or other gastro-intestinal disturbances The dose is then reduced [illegible]

disturbed the creosote should be stopped at once Creosote carbonate is sometimes substituted for creosote in doses twice or thrice the size. Creosote is sometimes vaporized by igniting it, and the patient, breathing the fumes in a closed room, coughs violently and expectorates profusely; King quoted authors who have found these "baths" useful when given two or three times daily.

Climate.—Climatic change sometimes benefits the patient, and it is not always the warm dry climate which is best, for some individuals do well at the seashore or in the mountains

Desensitization.—Watson and Kibler (1938) reported considerable improvement in some of their cases in which desensitization therapy was employed, most common sensitizations were to feathers, pollens, orris root, house dust and wool, but there were a few cases in which foods were said to have been the most important factor

ABSCESS OF THE LUNG

Abscess of the lung may follow a severe bruise of the chest wall or a penetrating wound of the lung, or it may occur during the course of chronic pulmonary tuberculosis, or it may occur as a sequela of pneumonia, especially the influenzal type of pneumonia. Its occurrence following operations in [illegible]

for pulmonary resection, for the primary bronchial dilatation cannot be affected by nebulization therapy and therefore patients who receive only this type of therapy remain subject to all the hazards of a deformed bronchial tree. Olsen (1946) said that at the Mayo Clinic penicillin in concentration of 10,000 units per cc. is employed, the patient using 20 to 30 cc. of the solution for aerosolization during each day; a striking reduction in the amount of sputum occurs in about half the cases. Kay *et al.* (1947) said that in no patient with advanced bronchiectasis will the employment of penicillin cause the sputum to disappear completely and that when penicillin is discontinued symptoms invariably recur in a short period of time.

Streptomycin.—Olsen (1946) reported the employment of aerosolized streptomycin in nine cases in which penicillin aerosol had been used for some time without obtaining the desired reduction in the volume of sputum. Five hundred thousand units of streptomycin dissolved in 20 cc. of physiologic saline solution was nebulized each day, being sometimes employed together with 200,000 units of penicillin, it being found that penicillin sodium and streptomycin hydrochloride can be combined very satisfactorily for nebulization. In each of these nine cases the gram-negative bacteria disappeared rapidly from pulmonary secretions and the reduction of volume of sputum was almost immediate. Although none of the patients became entirely sputum-free, the remaining sputum lost its purulent character and the immediate results were most satisfactory. Both penicillin and streptomycin may be instilled directly into the bronchial tree in a manner similar to that employed in the instillation of iodized oil for bronchography. Several observers have expressed the opinion that this sort of intra-tracheal treatment is sometimes a valuable adjunct to nebulization.

Sulfonamides.—Thomas *et al* (1945) reported best results from the sulfonamides when their employment was combined with the management of the major allergy that was found to be present in a large proportion of their series of patients. Olsen (1946) said that the employment of sulfonamides at the Mayo Clinic had not been very gratifying except in the preparation of patients for operation, in which case it was thought that they were helpful in prevention of postoperative complications, but not as helpful as penicillin.

Lipiodol Injections.—The oil is introduced either through the bronchoscope or by injection from a syringe, or it is inhaled from the mouth. All of these are special technics which of course cannot be learned from the pages of a book. Opinion varies as to the action of the oil: some say it dilutes the sputum [illegible] displaces the sputum [illegible] irritation [illegible] e not, it [illegible] ions are [illegible] o King [illegible] st on continuation of [illegible] erred to the dramatic [illegible] ic removal of copious [illegible] improvement occurs [illegible] months usually calls for repetition of the bronchoscopic treatment. Olsen (1946) said that bronchoscopy should be performed at least once in every case of bronchiectasis on the chance that bronchial obstruction such as by foreign bodies, tumors, broncholiths or bronchostenosis, may be discovered.

the pain disappears and dyspnea develops; it is not in order in this book to describe the numerous other physical diagnostic signs of effusion. Occasionally a patient feels very little subjective distress whatever.

The immediate prognosis in both forms of pleurisy is good. A dry case usually clears up gradually in two to three weeks; a case with effusion is often protracted much beyond this period. However, the fact that an attack of pleurisy is looked upon as presumptive evidence that the individual who *suffers it is tuberculous makes the disease of much more serious import.* Some physicians of vast experience maintain that *all* cases of pleurisy are tuberculous, others hold that all cases not accompanied by the signs of a known [illegible]

always make a diagnosis of tuberculosis in any patient who has pleurisy twice, whether with or without effusion Feldman and Lewis (1946) made the point that the frequent inability to isolate tubercle bacillus from the pleural fluid, [illegible]

patient, for they said that active cases of tuberculosis can exist in the lung and be directly responsible for the onset of effusion though the fluid remains sterile In Thompson's (1946) follow-up study of 190 cases of simple pleurisy with effusion it was found that subsequent tuberculosis was diagnosed in 12 per cent of the patients within the first year, in 8 per cent of the remainder within the second year, and in a total of 25 per cent within five years.

Boerhaave (1668–1738) was the first to show that pleurisy is an affection of the pleura alone

THERAPY

The patient with dry pleurisy should be kept at rest—indeed he will impose the most absolute immobility upon himself, usually lying on the affected side with the shoulder depressed and the arm stretched along the body. Compresses are hardly worth using for relief of the pain The best measure is the application of adhesive plaster strips (2-inch width) with the chest in the expiratory position They should pass from the vertebral column to the midline in front, at right angles to the column, not slanting with the ribs; begin below and let each strip slightly overlap its predecessor The cough does not usually require special treatment if the affected side is immobilized in this way. In severe cases, 1 grain (60 mg) of codeine sulfate, or if necessary ¼ grain (15 mg) of morphine sulfate or 1/32 grain (2 mg) of dilaudid hydrochloride, should not be withheld in the beginning It is doubtful if there is any warrant for the belief that the administration of calcium salts or of parathyroid extract will prevent effusion or promote its resorption

Shaw (1935) pointed out the danger of inducing basal atelectasis, especially in elderly individuals, through partial immobilization by strapping or as a result of respiratory depression consequent upon the use of opiates. In two instances in which atelectatic pneumonia had already developed, he induced shallow pneumothorax with 200 to 250 cc. of air, and obtained almost immediate relief and the recovery of both patients, in whom it had been felt that the prognosis was extremely grave at the time of making the injections. He believed that the usual objections to artificial pneumothorax—risk of second-

NEPHRITIS AND NEPHROSIS

Acute diffuse glomerular nephritis usually makes its appearance, abruptly or insidiously, in children or young adults several days or weeks after apparent recovery from an upper respiratory infection or from one of the acute streptococcic infections, such as tonsillitis, scarlet fever, rheumatic fever, or erysipelas Many observers now believe that the attack is the expression in the kidney of a widely diffused vascular inflammation, which may be allergic in nature. Cases occurring during a subacute bacterial endocarditis are usually looked upon as "focal" rather than "diffuse," the differentiation being made on the smaller number of glomeruli found to have been involved in the rare specimens that come to autopsy, plus the absence of hypertension and edema. In the common or diffuse form there are present both edema and hypertension, but the former is rarely of the marked pitting sort seen in nephrosis, and the hypertension is usually not inordinately high and very rarely may not be present at all There is more or less albumin in the urine but the characteristic feature of these cases, in addition to the hypertension, is the presence of red blood cells and red cell casts often enough to cause the urine, which is diminished in amount, to have a smoky brown color.

Ordinarily the acute death rate may be reckoned at 5 to 10 or 12 per cent. The prognosis as regards ultimate recovery without permanent sequelae, though now admitted to be better than formerly believed, varies considerably. Cass (1939), studying eighty-eight cases in England, found that the condition ultimately became a chronic one in 32 0 per cent of those who had not died in the acute attack, Snoke's (1939) figure for a large series of cases in San Francisco was 47 2 per cent, while for a series in Rochester, N. Y., it was 13.7 per cent, here in Milwaukee, Murphy and Peters (1942) reported the following outcome in 205 cases studied during a ten-year period: 12.6 per cent died during the acute stage, 17 0 per cent were discharged recovered but were not reexamined, 34 1 per cent recovered and were found healed upon reexamination; 9 2 per cent were found latent upon reexamination; 26 8 per cent became chronic nephritics Most clinicians are now in agreement that patients who experience the most turbulent onset often have the best outlook for complete recovery. Cases advancing toward chronicity frequently develop subacute exacerbations during which there is some elevation of temperature and the urine is clouded with blood and casts, but as the glomeruli are gradually destroyed during months and years the urine contains less blood and fewer erythrocytic casts, and finally nitrogen retention, manifested by rise in blood urea and creatinine, makes its appearance, foretelling uremic termination—though it has been remarked that in all *fatal* cases of chronic nephritis characterized by severe nitrogen retention there is an acidosis severe enough in itself to be the actual cause of death. It has also come to be increasingly recognized in recent years that severe anemia is an accompaniment of decreasing renal efficiency, though it may also appear early in the acute cases. Marchand and Finch (1944) reported fatal spontaneous potassium intoxication occurring in two cases of uremia with renal failure and oliguria, and Dickes (1942), and Roen (1944), published studies indicating an inter-

ary pleural infection, of causing or increasing myocardial distress, of pleural shock and air embolism—are bogies with a very infrequent incidence.

When fluid appears in sufficient quantities to aggravate the condition of the patient it should be removed by paracentesis The indications for, and the technic of, this procedure are to be learned in an apprenticeship upon the wards and not from the pages of a book. Attempt should not be made to remove the effusion by diuresis or catharsis, for the fluid cannot return with sufficient rapidity through the inflamed serous membrane to make up for the loss of water by way of the kidney or bowel; the patient will thus only be weakened to no purpose. Blisters are also of little or no value.

The necessity for looking upon an individual who has once had an attack of pleurisy as a tuberculosis suspect is of the utmost importance, since by accepting such an attack as a sign from the gods that a readjustment of the mode of life is in order, we may sometimes entirely prevent the appearance of a frank pulmonary tuberculosis. Jones and Dooley (1946) said they believed that the treatment for tuberculous pleurisy with effusion should be as prolonged as for acute rapidly changing pulmonary tuberculosis and that the patient should be on strict bed rest for several months after all clinical and laboratory signs are normal.

LARYNGITIS

Acute laryngitis appears rather suddenly with a dryness and tickling in the throat and some pain on swallowing; oftentimes there is tenderness to pressure made upon the protruding portions of the voice box in the neck. The voice becomes husky and speaking is not only painful but is also provocative of extreme weariness. Cough may not be present in the beginning but it usually develops quite soon and *serves to eliminate* considerable amounts of mucus. Not infrequently the voice is completely lost during the few days' duration of the attack.

Laryngitis usually follows exposure to sudden changes of temperature, sudden climatic changes, inhalation of irritating materials, or excessive or faulty use of the voice. Occasionally the condition becomes chronic; in these cases there is nearly always a discoverable source of chronic infection in the *nasopharynx.*

THERAPY

Rest of the body, and especially rest of the voice, are the most important
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... such as is described
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The use of drugs to control the *cough* is doubtfully ...
... a benign purpose: when it becomes too severe, however, the prepa-
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bed when the hypertension and edema have disappeared even if there are still urinary abnormalities, for he made the point that albumin and some blood may persist in the urine for three to six months longer even in those who ultimately recover. Murphy and Rastetter (1938) felt that the persistence of hypertension and urinary and other laboratory findings after three months mark the transition into chronicity and that nothing is gained in keeping the patient in bed any longer.

to take the regular ward diet, only restricting sodium, and that the statistical results are as good as those obtained under strict regimens. Burke and Ross (1947), in reviewing the therapy of ninety cases of acute glomerular nephritis in children, said that they used a relatively high-protein, high-carbohydrate, low-fat, salt-free diet and gave fluids as desired.

Edema.—It is impossible in the present state of our knowledge to direct any measures toward the relief of the edema of acute glomerular nephritis since it is due to increased capillary permeability resulting from bacterial toxin injury. Diuretics are not indicated but salt restriction is of course advisable since the more sodium in the extravascular spaces the more water will be held. The edema of acute tubular (degenerative) nephritis, with reduction in plasma proteins, requires to be handled in principle as the edema of chronic nephritis (see below.)

Nonuremic Convulsions.—This type of convulsion, of rather frequent occurrence in children, is characterized by the premonitory symptoms of sudden violent headache and visual disturbances, central vomiting, and a rapid rise in blood pressure, and is often followed by coma, a Kernig and a Babinski sign and occasionally transient paralytic symptoms. The syndrome, not being due to the retention of nitrogenous products and hence not being true uremia, is considered to result from cerebral edema and angiospasm; it is definitely relievable by depleting measures. Burke and Ross (1947), in reviewing the treatment of ninety cases of acute glomerular nephritis in children, said they

rule of thumb dosage for magnesium sulfate in hypertensive encephalopathy is 0.4 cc. of 25 per cent solution per kg. of body weight. Alarming toxic symptoms rarely follow the use of magnesium sulfate parenterally, but it is well to

esting relationship between the blood phenol level and the outcome in uremia; considerable disturbances in calcium metabolism are also sometimes seen. Lipemia, often very marked, tends to decrease in the terminal stages of the disease and the plasma lipid content may fall below normal just before death.

The striking characteristics of *tubular (degenerative) nephritis* which distinguish it in its *pure* form from the glomerular type, are hyaline, waxy and fatty casts but no blood or blood casts in the urine, marked and persistent edema, and albuminuria without hypertension or nitrogen retention. This type may also appear acutely in children in the course of streptococcal or other blood stream invasions, or as a mild form complicating Asiatic cholera, diphtheria, malaria, syphilis, typhus, yellow fever and possibly other infectious diseases. It is the nephritis sometimes caused by mercury and the arsenicals, also the nephritis seen in the late toxemia of pregnancy. If, in addition, there is observed an increased blood cholesterol, refractile globular bodies in the urine, a low metabolic rate, low serum protein with a marked disturbance in the ratio of serum albumin to serum globulin, and a tendency toward a protracted course with relatively frequent complete recoveries or death from intercurrent infection without the appearance of signs of severe inflammatory renal disturbance—in these cases the diagnosis of *lipoid nephrosis* is made, which is considered by some observers to be a rare entity not directly related to inflammatory nephritis.

The type of kidney disease known as *arteriolosclerotic nephritis* is only one element in the cardiovascular-renal syndrome, which begins with "essential" hypertension, progresses to arteriolar disease of the body as a whole and not solely of the kidneys, and ends often in cardiac or apoplectic death before kidney complications of a serious nature have appeared. The urine is much increased in amount and low in specific gravity and contains often only a small amount of albumin and a few hyaline casts. Edema is not a usual feature of the pure form, but ultimately uremia appears in association with the slowly increasing nitrogen retention. More rapidly progressive cases are designated "malignant."

So far as is yet known, the first description of kidney disease was that of [illegible] that certain cases of [illegible]

[illegible] contracted kidney, [illegible] of Harvey (1578- [illegible] re laid the founda- [illegible] rect his anatomico- [illegible]

THERAPY OF ACUTE NEPHRITIS

Rest.—It is the consensus of course that the patient should be in bed and at complete rest during the early stages, but there is difference of opinion regarding how long this absolute rest should be imposed. Page (1940), it seems to me, has been for keeping the patient in bed as long as this may be easily done, but Goldring (1941) believed that he should be allowed out of

tured from some focus. The results indicated that under the drug the foci of infection cleared up more rapidly, the signs of renal damage disappeared more rapidly, exacerbations of the nephritis following tonsillectomy occurred less frequently, the duration of edema and hypertension was reduced, and the proportion of clinical recoveries was greater (74.3 per cent in the thirty-nine patients followed for at least two years). However, Rapoport *et al.* (1946) used sulfanilamide in a group of thirty-three children, a group of forty children not so treated acting as controls, they found that the sulfanilamide therapy appeared to be without influence on the course and duration of the acute glomerulonephritis in this study. Aside from the fact that diminished renal function enjoins caution, the nephritis itself would not seem to contraindicate the use of sulfanilamide, but it would seem to be the part of wisdom to be very hesitant regarding the use of the other members of this series whose tendency to cause renal damage through settling out of the acetylated product is well known. Sen (1946) reported the use of penicillin in twelve cases of acute nephritis in children chosen for the reason that they were *in extremis* and had failed to respond to any other form of treatment; eleven of the twelve children recovered in the sense that fever, edema, casts, albumin and blood cells all disappeared.

Goldring (1941) undoubtedly expressed the consensus when he said that one should wait four to six months before removing suspected foci of infection even if they are obviously purulent; early removal invites recurrence of the nephritis

THERAPY OF CHRONIC NEPHRITIS (AND NEPHROSIS)

Edema

High Protein Diet.—The chief surviving hypotheses in explanation of

braced this viewpoint Second, that there occurs a general metabolic disturbance of such nature that there is a shift in the plasma proteins toward the coarser globulin fraction, albuminuria then resulting when the kidneys excrete this foreign "denatured" protein in a quite physiologic way and without any increase in their permeability, there is much disagreement regarding this concept at present. Fortunately, in practical therapeutics it does not really matter which of the "explanations" is the correct one, for the albumin is there in the urine regardless of how it arrived, and the patient is likewise often edematous. This association of albuminuria with edema is rather well understood nowadays· when the total protein of the plasma falls as a result of albuminuria, the ratio of albumin to globulin in the blood is reversed, the proportion of globulin to albumin becoming greater, however, the large globulin molecule exerting a lower osmotic pressure than did the smaller albumin molecule which it replaces, the total osmotic pressure within the

on the needs of a normal healthy individual of the patient's age, height and weight, though in frequent instances it may be necessary for a time to exceed the normal daily amounts of protein per kilogram body weight. However, the optimal amount for adults seems to be between 70 and 100 gm., for above

be prepared to combat respiratory depression by the slow intravenous injection of a few cubic centimeters of 25 per cent calcium chloride solution. Hypertonic dextrose may be given intravenously instead of magnesium sulfate; 25 to 100 cc. of 50 per cent *solution are most often used. An* objectionable feature of this use of dextrose is that it frequently induces a high secondary rise in cerebrospinal fluid pressure. Both Page (1940) and Lueth (1941) spoke favorably of the intravenous administration of 50 per cent sucrose solution, giving from 50 to 250 cc. but injecting very slowly if cardiac failure is impending. In rare instances sucrose seems capable of causing tubular degeneration, but the effect is only transient and it would seem from the work of Lindberg *et al.* (1939) is not likely to alter renal function. Venesection may be of value; spinal puncture is definitely of aid if coma supervenes—but Goldring (1941) warned that the fluid *must not be permitted to run out fast.*

Hypertension.—In most instances the hypertension *per se* is transient and does not call for treatment directed specifically toward its relief, which is fortunate since we know so little of its causation. In some instances magnesium sulfate parenterally, as in treatment of convulsions (see above), relieves hypertension.

Heart Failure.—It is the general impression that myocardial involvement is rare in acute glomerular nephritis, but Whitehill *et al.* (1939) found the signs of circulatory insufficiency very frequently in the moderately severe and usually in the very severe cases among their 138 patients. La Due's (1944) study indicated the possible importance of hypertension in the pathogenesis of this type of congestive failure, while Odel and Tinney (1943) pointed out that patients who die during the acute phase of glomerulonephritis may die from heart failure. This type of congestive heart failure responds to digitalis in the usual way (see Index for methods).

Anuria.—Anuria is not a common occurrence, which is fortunate for it is usually accompanied by uremia and is likely to be fatal. Page's (1940) recommendations for treatment may be outlined as follows: (a) Catheterize to be sure there is no obstruction. (b) Give 50 per cent dextrose intravenously (c) Try a hot bath lasting thirty minutes or more, simultaneously administering 400 to 500 cc. of fruit juice. (d) If there is acidosis, give sodium bicarbonate by vein. (e) If all these measures fail and little or no urine has been passed for three days, decapsulation of the kidney should be tried. Some *men increase the fluid intake* to 2000 or even 3000 cc. per day, regardless of the presence of edema or the danger of inducing it. Goldring (1941) ex- [illegible] urine flowing again, [illegible] deficient blood flow [illegible] see how the administration of hypertonic solutions of sucrose or dextrose *would correct* the functional disturbance. It is significant, too, that decapsulation is performed much less frequently now than formerly.

Uremia.—See under the same heading in the therapy of Terminal Nephritis In acute glomerular nephritis the symptoms are often alarming but the condition is apparently not of serious moment since as many complete recoveries seem to occur in those who develop an extremely high nonprotein nitrogen as in those who do not.

Treatment of Infections.—Williams, Longcope, and Janeway (1942) used sulfanilamide in forty-two patients in the acute stage of nephritis, nearly all of them being patients from whom beta hemolytic streptococci had been cul-

tured from some focus. The results indicated that under the drug the fo[ci] of infection cleared up more rapidly, the signs of renal damage disappeare[d] more rapidly, exacerbations of the nephritis following tonsillectomy occurre[d] less frequently, the duration of edema and hypertension was reduced, and the proportion of clinical recoveries was greater (74.3 per cent in the thirty-nine patients followed for at least two years). However, Rapoport *et al.* (1946) used sulfanilamide in a group of thirty-three children, a group of forty children not so treated acting as controls; they found that the sulfanilamide therapy appeared to be without influence on the course and duration of the acute glomerulonephritis in this study. Aside from the fact that diminished renal function enjoins caution, the nephritis itself would not seem to contraindicate the use of sulfanilamide, but it would seem to be the part of wisdom to be very hesitant regarding the use of the other members of this series whose tendency to cause renal damage through settling out of the acetylated product is well known. Sen (1946) reported the use of penicillin in twelve cases of acute nephritis in children chosen for the reason that they were *in extremis* and had failed to respond to any other form of treatment; eleven of the twelve children recovered in the sense that fever, edema, casts, albumin and blood cells all disappeared.

Goldring (1941) undoubtedly expressed the consensus when he said that one should wait four to six months before removing suspected foci of infection even if they are obviously purulent, early removal invites recurrence of the nephritis.

THERAPY OF CHRONIC NEPHRITIS (AND NEPHROSIS)

Edema

High Protein Diet.—The chief surviving hypotheses in explanation of albuminuria are the two which follow. First, that functional or actual retrogressive changes in the glomerular capillaries permit the passage of albumin through this filter which normally holds it back; many observers have embraced this viewpoint. Second, that there occurs a general metabolic disturbance of such nature that there is a shift in the plasma proteins toward the coarser globulin fraction, albuminuria then resulting when the kidneys excrete this foreign "denatured" protein in a quite physiologic way and without any increase in their permeability; there is much disagreement regarding this concept at present. Fortunately, in practical therapeutics it does not really matter which of the "explanations" is the correct one, for the albumin is there in the urine regardless of how it arrived, and the patient is likewise often edematous. This association of albuminuria with edema is rather well understood nowadays: when the total protein of the plasma falls as a result of albuminuria, the ratio of albumin to globulin in the blood is reversed, the proportion of globulin to albumin becoming greater; however, the large globulin molecule exerting a lower osmotic pressure than did the smaller albumin molecule which it replaces, the total osmotic pressure within the vessels is lessened, and fluids pass out into, and remain in, the tissue spaces. This comprises the rationale of the high protein diets of today. The actual computation of diets (food value tables in Diabetes) can be based usually on the needs of a normal healthy individual of the patient's age, height and weight, though in frequent instances it may be necessary for a time to exceed the normal daily amounts of protein per kilogram body weight. However, the optimal amount for adults seems to be between 70 and 100 gm., for above

this loss of appetite usually occurs; in children the rate of 3 gm. per kilogram (2.2 pounds) of body weight seems optimal to many observers, but Loeb (1947) said that the results of forced protein feeding had been disappointing; beyond giving the patient enough protein to maintain nitrogen balance and to restore the body protein lost, in his opinion there is little to be said in favor of excessive (3 or more gm. per kg.) protein feeding, which might even increase the renal damage The sample menus offered in Table 22 contain usually adequate amounts of protein; as there indicated, it should be preferably given in the form of foods with high biological value, such as meat (there are no differences between red and white meat), milk, cheese, fish, and eggs. As protein is deposited in the tissues it may increase the edema for a while until the slowly rising serum proteins (a process which may require several months) draw it out again and diuresis begins. There is no contraindication to the usual allowances of carbohydrates and fats. In many instances it is probably advisable to add supplementary vitamins. Bruger *et al.* (1939) found that alcohol in moderate amounts rarely augments proteinuria and sometimes induces moderate diuresis even in the presence of considerable impairment of renal function; in spite of these observations, however, I imagine most men will continue to feel justified in greatly restricting the use of alcohol in their patients.

Water, Salt, Acid and Base Allowances.—As above stated, edema results from the loss of proteins from the blood in a patient with albuminuria, but this is not the sole explanation for the water imbalance since it has been amply demonstrated that in renal edema a part of the water-logging is due to a retention of chlorides Whether this retention is due to inability of the damaged kidneys to excrete these salts, or whether they are not excreted simply because they are held by the extrarenal tissues, is still a moot point. At any rate, sodium chloride when administered is retained and edema increases if the nephritic state is at all severe or advanced. An absolutely salt-free diet is certainly not advisable for the following reasons (a) such a diet is woefully unpalatable and causes nausea and vomiting, headache and leg ache, and a host of other symptoms, (b) moderate reduction is easier and in the end more effective because it can be continued for a long period

The average daily salt ration in America is about 10 gm., water intake probably 2000 cc The salt can be considerably reduced without difficulty since most of it derives from its addition to foods during preparation, most raw foods being salt-poor. The principal exceptions that are likely to be included in the average dietary are milk, butter, cheese, preserved meats, fish and breads. Allowing any foods desired but forbidding the use of salt either in kitchen or dining-room, means permitting 3 gm , or perhaps slightly less, daily, this may be raised by actual additions of salt, lowered by omitting milk, salted butter or any other of the worst offending articles Condiments, such as pepper, mustard, vinegar, lemon juice, spices, garlic, onion, etc , may be used and are not harmful to the kidney.

Ample experience has now shown that water restriction is not necessary, for even large volumes of water given without salt are excreted without difficulty; [illegible] the restriction of sodium salts, particularly sodium chloride, which is [illegible]

tice has arisen of substituting other salts for [illegible]

TABLE 22.—HIGH-PROTEIN, LOW-SODIUM, HIGH-POTASSIUM DIET WITH ACID ASH FOR USE IN EDEMA (After BARKER)

Ingredients

Fruits.
3 servings daily, fresh or stewed, but should include either prunes, plums, cranberries or currants once daily

Vegetables
2 large servings daily, especially beets, carrots, Brussels sprouts, yellow corn, kohlrabi, lettuce, mushrooms, peas, spinach, kidney beans, parsnips.

Meat:
2 servings daily.

Eggs·
2.

Milk·
1 glass.

Cream·
½ glass.

Butter·
Salt-free, 6 squares

Cereal
Oatmeal or wheatena; farina, puffed wheat or rice occasionally

Bread.
Graham bread, 3 large slices or 6 small slices daily.

Rice, macaroni or spaghetti:
1 serving daily.

Potato
1 serving

Jelly, preserves or honey:
2 level tablespoonfuls

Sugar
Ad libitum—at least 1 tablespoonful.

Sample Menus

1	2	3
Breakfast	*Breakfast*	*Breakfast*
Stewed currants	Plums	Stewed prunes
Oatmeal	Wheatena	Farina
Two poached eggs	Scrambled eggs	Soft cooked eggs
Graham toast	Graham toast	Graham toast
Sweet butter	Sweet butter	Sweet butter
Honey	Jelly	Honey
Cream	Cream	Cream
Sugar	Sugar	Sugar
Dinner	*Dinner*	*Dinner*
Roast beef	Broiled steak	Broiled lamb chop
Mashed potatoes	Buttered macaroni	Buttered spaghetti
Buttered beets	Stewed tomatoes	Buttered spinach
Sliced peaches	Banana salad	Grapefruit cup
Graham bread	Graham bread	Graham bread
Sweet butter	Sweet butter	Sweet butter
½ glass milk	½ glass milk	½ glass milk
Supper	*Supper*	*Supper*
Broiled chicken	Broiled liver or sweetbreads	Broiled whitefish
Buttered rice	Baked potato	Mashed potatoes
Jelly	Celery salad	Buttered Brussels sprouts
Lettuce salad	Cherries	Pineapple and nut salad
Orange cup	Graham bread	Graham bread
Graham bread	Butter	Sweet butter
Sweet butter	Jelly	Jelly
½ glass milk	½ glass milk	½ glass milk

Notes

[illegible] of viosterol.

Coffee or tea, 1 cup daily.

This diet is designed for the treatment of convalescent and ambulatory patients. Very ill patients are to be given the same foods but in smaller amounts.

chloride, 5 to 15 gm. daily, potassium chloride, 5 to 10 gm daily, calcium chloride, 10 to 20 gm daily, ammonium sulfate, 2 to 6 gm. daily, or even 100 to 200 cc. daily of N/10 hydrochloric acid. Potassium chloride has had the greatest vogue but many individuals object to its metallic taste. Using a diet with a high acid ash, which is easily accomplished when high-protein feeding is being employed, is also of diuretic value.

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diet which is adequate in every respect except that small supplementary vitamin additions (vitamin D, in particular, is deficient) had best be made now and then. The total amounts of specific minerals agree closely with Sherman's average of 150 American dietaries except in the inverted ratio of potassium to sodium. The diet is properly high in protein and has an acid ash. No sodium chloride is used in either kitchen or dining room, but the patient is given 5 gm , occasionally more, of potassium chloride crystals in a salt shaker each morning, with this he salts his food and at the end of the day places the remainder in water and drinks it. In the main no ill effects have followed in patients who have been upon this regimen for several years; one of Barker's patients with pronounced nephrosis required 10 gm. potassium chloride daily to remain edema-free. Winkler *et al* (1941) considered it unlikely that the potassium ion can cause poisoning when given by mouth under the conditions here obtaining, since they felt that even the most severely damaged nephritic kidney continues to excrete potassium. However, Keith *et al.* (1943) felt that potassium salts should not be used in patients with nephritic edema and a concentration of urea in the blood of more than 100 mg. per 100 cc., for in some of these patients there may be a lessened tolerance for potassium and even an increased value for potassium in the serum. This type of acid-ash dieting does not alter the acid-base balance of the body.

Diuresis.—*Diuretic Drugs* —The agents most often used in nephritic edema are potassium nitrate and a mercurial One often hears the statement that the mercurials are contraindicated if there is renal pathology, but many leading clinicians feel that they may be used with impunity if good care is taken; the use of these agents is thoroughly discussed in Congestive Heart Failure.

Acacia —Acacia lost most of its early friends very quickly because of the severe, though admittedly rare, reactions sometimes accompanying its use

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diuretic salts in their treatment of the nephrotic state of chronic glomerulo-

is given and then the latter is injected slowly (forty-five to seventy-five minutes) intravenously in an average adult dose of 500 cc. of a 6 per cent solution in 0 06 per cent sodium chloride solution. Injections are usually given every day or on alternate days for at least three or four times. Sometimes fever, urticaria and dyspnea or pain in the left chest occur as reactions. Smalley and Binger recognized no contraindication to the continuance of acacia treatments except the very rare occurrence of a severe allergic reaction—they did not see

the blood pressure remain at a higher level than that which existed before the injection nor did they see renal damage result from the use of acacia; in fact, they mentioned instances of a lowering of the blood pressure and improvement in renal function. It was their opinion also that the solution can be used without fear in patients who have severe hepatic cirrhosis.

Transfusion.—Whole blood transfusion is frequently resorted to when the edema is great enough to cause dyspnea Diuresis and a considerable diminution of distress are often obtained, effects which may persist several days

Plasma, Serum Albumin, Globin, Amino Acids.—It has been the general experience that even temporarily beneficial effects following the use of plasma are not often seen, the agent containing of course not only physiological salt solution but in addition a large amount of sodium from the citrate used in its preparation. However, surprisingly, Strumia *et al.* (1946) stated the [illegible] e, that it has the advantage of [illegible] tores, and that when properly [illegible] reactions. They found that it does not have to be concentrated in order to be effective and felt that the sodium chloride content can be considered a disadvantage only in a relatively small number of cases Aldrich (1947) also said he believes that the administration of plasma to patients early in the course of nephrosis who are not suffering from evident or hidden infections has a definite tendency to produce diuresis if given in large doses and repeatedly. Strumia *et al.* felt that salt-free human albumin offers no outstanding advantage over plasma to offset its higher cost Loeb (1947), discussing this matter, said that when the massive doses of albumin (usually 50 gm daily) necessary to induce diuresis are given, as much as 50 to 75 per cent of the material is excreted by the kidney To him it seemed possible that a very important part of the diuretic effect is a reflection of the choking of the renal tubules with reabsorbed albumin, *i e*, the tubules are temporarily damaged and their reabsorption of sodium salts and water thereby decreased. Loeb's viewpoint [illegible]

[illegible] made relatively cheaply from erythrocytes left over from the preparation of plasma, but of course large amounts of such erythrocytes will not be available regularly during peace times as they were during War II MacFadyen's (1947) review of the use of amino acids in nephrosis indicated clearly that the subject is still in the stage of clinical experimentation.

Thyroid Substance.—Low basal metabolic rates have been recorded a number of times in nephritis, but a reclassification of the disease which would ascribe fundamental significance to these observations is probably not warranted upon the basis of any evidence yet accumulated. In his exhaustive review, Leiter (1931) [illegible] tha [illegible] dic [illegible] nature of the malady In nephrotic cases a number of observers have reported the favorable production of diuresis by the employment of enormous doses of thyroid substance The results are by no means always obtained, but the fact seems to [illegible]

chloride, 5 to 15 gm. daily, potassium chloride, 5 to 10 gm. daily, calcium chloride, 10 to 20 gm daily, ammonium sulfate, 2 to 6 gm. daily, or even 100 to 200 cc. daily of N/10 hydrochloric acid. Potassium chloride has had the greatest vogue but many individuals object to its metallic taste. Using a diet with a high acid ash, which is easily accomplished when high-protein feeding is being employed, is also of diuretic value.

The accompanying table (Table 22) shows the type of dietary regimen that Barker and his associates at Northwestern University use in complying with all the requirements discussed above. Briefly, the patient is given a liberal diet which is adequate in every respect except that small supplementary vitamin additions (vitamin D, in particular, is deficient) had best be made now and then. The total amounts of specific minerals agree closely with Sherman's average of 150 American dietaries except in the inverted ratio of potassium to *sodium* The diet is prope

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is given and then the latter is injected slowly (forty-five to seventy-five minutes) intravenously in an average adult dose of 500 cc. of a 6 per cent solution in 0.06 per cent sodium chloride solution Injections are usually given every day or on alternate days for at least three or four times Sometimes fever, urticaria and dyspnea or pain in the left chest occur as reactions Smalley and Binger recognized no contraindication to the continuance of acacia treatments except the very rare occurrence of a severe allergic reaction—they did not see

the blood pressure remain at a higher level than that which existed before the injection nor did they see renal damage result from the use of acacia; in fact, they mentioned instances of a lowering of the blood pressure and improvement in renal function. It was their opinion also that the solution can be used without fear in patients who have severe hepatic cirrhosis.

Transfusion—Whole blood transfusion is frequently resorted to when the edema is great enough to cause dyspnea Diuresis and a considerable diminution of distress are often obtained, effects which may persist several days.

Plasma, Serum Albumin, Globin, Amino Acids—It has been the general experience that even temporarily beneficial effects following the use of plasma are not often seen, the agent containing of course not only physiological salt solution but in addition a large amount of sodium from the citrate used in its preparation. However, surprisingly, Strumia *et al* (1946) stated the opinion that plasma is generally very effective, that it has the advantage of adding at least temporarily to the protein stores, and that when properly used it is practically free from the danger of reactions They found that it does not have to be concentrated in order to be effective and felt that the sodium chloride content can be considered a disadvantage only in a relatively small number of cases. Aldrich (1947) also said he believes that the administration of plasma to patients early in the course of nephrosis who are not suffering from evident or hidden infections has a definite tendency to produce diuresis if given in large doses and repeatedly Strumia *et al.* felt that salt-free human albumin offers no outstanding advantage over plasma to offset its higher cost. Loeb (1947), discussing this matter, said that when the massive doses of albumin (usually 50 gm. daily) necessary to induce diuresis are given, as much as 50 to 75 per cent of the material is excreted by the kidney. To him it seemed possible that a very important part of the diuretic effect is a reflection of the choking of the renal tubules with reabsorbed albumin, *i.e.*, the tubules are temporarily damaged and their reabsorption of sodium salts and water thereby decreased. Loeb's viewpoint

made relatively cheaply from erythrocytes left over from the preparation of plasma, but of course large amounts of such erythrocytes will not be available regularly during peace times as they were during War II. MacFadyen's (1947) review of the use of amino acids in nephrosis indicated clearly that the subject is still in the stage of clinical experimentation.

Thyroid Substance—Low basal metabolic rates have been recorded a number of times in nephritis, but a reclassification of the disease which would ascribe fundamental significance to these observations is probably not warranted upon the basis of any evidence yet accumulated In his exhaustive review, Leiter (1931) expressed doubt that the incidence of such rates is any greater than might be expected to occur secondarily to undernutrition, therapeutic diets, inactivity and possibly other factors not directly related to the intimate nature of the malady. In nephrotic cases a number of observers have reported the favorable production of diuresis by the employment of enormous doses of thyroid substance The results are by no means always obtained, but the fact seems to be established that individuals exhibiting the low basal metabolic phase of the malady can sometimes tolerate astonishing amounts of this ordinarily very toxic agent. Leiter believes that this is not true hypo-

chloride, 5 to 15 gm. daily, potassium chloride, 5 to 10 gm. daily, calcium chloride, 10 to 20 gm. daily, ammonium sulfate, 2 to 6 gm. daily, or even 100 to 200 cc. daily of N/10 hydrochloric acid Potassium chloride has had the

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age of 150 American dietaries except in the inverted ratio of potassium to sodium. The di

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potassium ion can cause poisoning when given by mouth under the conditions here obtaining, since they felt that even the most severely damaged nephritic

some of these patients there may be a lessened tolerance for potassium and even an increased value for potassium in the serum. This type of acid-ash dieting does not alter the acid-base balance of the body.

Diuresis.—*Diuretic Drugs* —The agents most often used in nephritic edema are potassium nitrate and a mercurial One often hears the statement that the mercurials are contraindicated if there is renal pathology, but many leading clinicians feel that they may be used with impunity if good care is taken; the use of these agents is thoroughly discussed in Congestive Heart Failure.

Acacia.—Acacia lost most of its early friends very quickly because of the severe, though admittedly rare, reactions sometimes accompanying its use

in the bone marrow,

the agent is

Mayo Clinic,

said they use it very frequently in combination with a high protein diet and

state of chronic glomerulo-

wed by

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acacia

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thyroidism in spite of the rate, that a tolerance above normal may be found in other edematous states, and that the matters of absorption, destruction, and excretion need to be studied in view of the differences between this sort of reduced metabolism and that encountered in true myxedema.

Cathartics.—Some physicians favor the daily use of a saline cathartic, but the practice certainly makes it impossible to maintain any exact knowledge of the patient's ability to eliminate through the kidneys. Proprietary saline mixtures should not be used unless it is positively known that they contain no other salts than the nonabsorbable ones desired to produce the cathartic effect The saline cathartics are discussed in Colon Consciousness. It is worthy of note that Hirschfelder and Haury (1934) described a clinical syndrome of high plasma magnesium accompanied by somnolence and coma, which may be induced by the oral administration of Epsom salt in patients with renal insufficiency.

Mechanical Measures.—Extensive hydrothorax or abdominal ascites, if causing respiratory embarrassment, is usually relieved by paracentesis. Most men undoubtedly feel that the danger of infection with the Southey tubes is too great to warrant their employment. Acupuncture (six or more punctures in either extremity with an 18-gauge needle), and the making of long deep incisions, are the older methods and have their very great efficacy marred considerably by the many obvious disadvantages associated with causing the person and bed of the patient to be soaked in fluid; for the patient able to sit up with the feet in a small tub they are excellent, but of course here again there is the danger of infection. However, it is of interest to note that Blumberg and Cassady (1947) draw attention to the fact that intercurrent infections may favorably modify the picture; they said that in their own experience they had found infection with measles more effective in causing [illegible] therapeutic agent they had used [illegible] rs ago that the value of gentle [illegible] too much overlooked in this [illegible] the same opinion and stated his feeling that bed rest and no exercise are inadvisable for the edematous patient unless there are absolute indications for such immobility; the latter feeling is widely shared by clinicians nowadays

Hypertension

The hypertension of arteriolosclerotic nephritis is a part of the cardiovascular renal syndrome and from the therapeutic standpoint it is idle to attempt a separate consideration (see Essential Hypertension).

THERAPY OF TERMINAL NEPHRITIS

The beginning of the end is recognizable by appearance or intensification of the eyeground changes, intensification or perhaps initial appearance of hypertension, and laboratory evidences of reduction in renal function With the approach of uremia, edema may disappear because of the destruction of so many glomeruli that a high rate of protein loss cannot be maintained, often, however, it is replaced by the edema of congestive heart failure. The pathogenesis of uremic heart failure has not been satisfactorily explained

The chief aim of treatment at this time is to make it possible for the patient to enjoy life as much as he can until the end Restrictions should be relaxed and the relatives told of the state of affairs so that they can help as much as

possible. Page (1940) well said: "It is, I think, a therapeutic achievement when the patient walks into the hospital and dies a few days or weeks after admission"

Diet.—Nothing is to be gained by any special dietary restrictions at this stage so it is well to allow the patient to choose just about what he likes. Theoretically a moderately low protein intake would be desirable in order to keep down the nitrogen retention, but as a matter of fact if insufficient protein is supplied for satisfactory tissue nutrition the balance is obtained from endogenous sources and the end result is the same as regards nitrogenous products to be eliminated. The chief problem usually is to get the patient to eat enough of anything, for the appetite has usually much decreased at this stage; sometimes even the use of a small amount of wine or a cordial is justi-

washed out. It is therefore well to study the plasma chlorides if possible and to administer sodium chloride (the reverse of what had been done up to this time) in an amount of 3 or 4 gm. daily together with sufficient water so that they will be washed out and not retained to induce edema afresh The way has to be felt carefully in each case and if there is a complicating heart failure the administration of chlorides will simply have to be abandoned.

Hypertension.—There is nothing one can do about this after it has become permanent

Pallor.—Patients are often distressed by their ghostly appearance. Page (1940) counseled sunlight or plenteous use of the ultraviolet lamp to bolster morale

chronic uremia has usually been looked upon as a final incident in the course

a marked degree Indeed, many observers feel that the severity of the symptoms of advanced nephritis and uremia is directly proportional to the degree of acidosis and not always or exactly to the extent of nitrogen retention.

through vomiting, for in advanced nephritis the free hydrochloric acid in the stomach is often very small in amount Undernutrition is also well known

of figs, molasses and raisins

Itching.—This is often a most distressing symptom and one difficult to relieve. Sponging, not rubbing, with a hot solution of sodium bicarbonate followed by dusting with talcum powder, or the application of 1 per cent

menthol in alcohol, or an ointment of 1 per cent phenol, may be tried. Other measures are discussed under Portal Cirrhosis.

Nausea and Vomiting.—I have never seen or heard of measures really effective in checking this vomiting, though of course the whole gamut of usual procedures is run: ice-sucking, sedatives, fresh air, etc. Correction of acidosis is the best preventive.

Convulsions.—In accordance with the belief (which is probably wrong) that it is the high nonprotein nitrogen content of the blood *per se* which induces the fatal termination in uremia, sweating would be theoretically indicated because the perspiration contains 30 per cent more of these retention products than does the blood. However, even though induced only by the use of hot-water bags and plenty of blankets, sweating is a very debilitating activity. A hypodermic of $\frac{1}{12}$ grain (5 mg) of pilocarpine nitrate is very effective in bringing out the perspiration, but it also not infrequently causes vomiting and hiccup, and may bring about collapse with a very slow pulse. [illegible]

Calcium may be employed as in tetany, but not parathyroid extract unless the necessity seems very urgent, for there is some evidence that the activity of the parathyroid glands is increased in chronic nephritis. Ordinary restlessness and even delirium may be combated with the sedatives and hypnotics (discussed under Insomnia), but morphine or dilaudid may have to be resorted to. Winkler *et al.* (1942) found the slow intravenous injection of 500 cc. of 2 per cent magnesium sulfate a safe procedure of some value in preventing and controlling these convulsive seizures, though they said the effects were neither certain nor dramatic following a single injection, a second injection always checked the convulsion, but after two such injections the magnesium concentration in serum sometimes became so high that its depressant effects on the nervous system were manifest. The correction of acidosis is a powerful weapon against recurrence of the convulsions When true uremic coma supervenes there seems to be nothing to do that is worth the doing.

DISTURBANCES CAUSED BY EXCESSIVE HEAT

HEAT EXHAUSTION

This, the most common form of disturbance caused by an excessively warm environment, is known in the South as "a touch of the sun" or "overcome by the heat." There may be prodromal symptoms of weakness, headache and constipation for a few days, but usually the individual suddenly becomes acutely sensitive to the oppressive atmospheric conditions, grows pale, with a clammy skin, has disturbances of vision, feels very weak and perhaps nauseated, and either crumples down in the sun or manages to drag himself into the shade before collapsing; the pulse is fast and weak, the respirations rapid and shallow, the pupils dilated, temperature normal or subnormal, urine scant Sometimes there are associated heat cramps (see below). Mortality from this type of heat stroke is very low, but the patient often recovers very slowly and is thereafter likely to be unusually sensitive to high temperatures Morton's (1944) experience over a period of years in Iraq left him with the impression that the type of individual particularly prone to develop heat exhaustion is the lean, anxious, spare person with a low systolic blood pressure.

THERAPY

The patient must be taken to the coolest place available and much of his clothing should be removed Attempt should be made to get him to drink copiously of sweetened fluids with sodium chloride added. In instances in which there has been excessive vomiting, Morton (1944) enjoined the intravenous administration of physiologic saline solution with dextrose. If the pulse remains rapid and weak for long, one of the stimulants (see Index) may be advantageously used Occasionally in these cases the temperature falls quite far below normal and it becomes necessary to apply external heat and administer hot drinks; one should be careful here as a sudden high rise of temperature may be induced

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HEAT STROKE

(Heat Retention)

The severe and frequently fatal form of disturbance caused by excessive heat is characterized by a brief prodromal period not easily distinguishable from that [illegible]

found to be contracted and the conjunctivae injected. In many cases involun-

tary passage of characteristically foul feces takes place and the patient's body odor also becomes offensive. Muscular twitchings and rolling of the head are common; *sometimes epileptiform convulsions take place* As death approaches evidences of pulmonary edema are sometimes to be found In a study of the hemorrhagic phenomena sometimes associated with *heat stroke*, and most

to this type of heat stroke; Bulmer (1943) reported that in Libya all the

from his experience in Iraq that *the obese, thick-necked individual* with a high systolic blood pressure is the type most likely to develop heat stroke.

Tenner (1942), Buss (1943), Freeman and Dumoff (1944), and Nayer (1945) have recorded instances in which permanent central nervous system residuals followed recovery from severe heat stroke.

THERAPY

It is imperatively necessary to reduce the temperature of this patient as rapidly as possible; Morton (1944) said that although short periods of temperatures as high as 112° F. (44 4° C.) or more have been followed by recovery, he was doubtful that if the temperature had remained at 108° F. (42.2° C.) or over for more than two hours survival could take place. The patient should *be encouraged to drink large quantities of fluids containing* glucose and sodium chloride, but Morton felt that since these patients are not usually dehydrated and are often suffering from a failing circulation the decision to use intravenous saline should be very carefully weighed. However, Nayer (1945) felt that since considerable body salt has often been lost, a slow intra*venous drip of isotonic sodium chloride would appear to be of some* value though the danger of pulmonary edema must always be taken into account. Borden *et al.* (1945) said that in the treatment of the more severe cases they preferred plasma rather than saline solution because of the ready diffusibility of the latter into the tissues They also found that the use of 100 per cent oxygen by mask proved advantageous. Oftentimes the use of cardiac and respiratory stimulants is required, and it is sometimes necessary to administer chloral and bromide by *rectum to control the convulsions.* Both Corr (1942) and Morton (1944) recorded single cases in which the withdrawal of spinal fluid controlled the convulsions The principal methods of effecting a quick lowering of the body temperature are the following:

(a) Water is sprayed onto the body from a fine nozzle preferably, or it *may be frequently* sponged over the body, meanwhile maintaining a constant current of air either by means of hand or electric fans There is no great advantage in using ice water as *tepid water will remove nearly as much* heat. This method has replaced all others in most hospitals and has the great advantage that it can be utilized anywhere since it does not depend upon the use of ice. When the rectal temperature reaches 102° F. (38.8° C.) evaporation may be stopped during a period of observation. The experience of Hearne with the British troops in Mesopotamia in War I was completely confirmed in War II, namely, that the cessation of sweating once it has been established is a valuable *sign of impending recurrence*, and that if these

patients are covered with a moist sheet and the fanning resumed, artificial perspiration will be established and recurrence sometimes averted.

(b) In this method the patient is placed in water cooled to 50° F. (10° C) by floating a cake of ice in it, and he is kept there until the rectal temperature falls to 102° F. (38.8° C.). After this temperature is reached the body will continue to lose heat in favorable cases even after removal from the water; sometimes the fall will go below the normal line. It is imperative that vigorous manual friction of the skin be made continuously while the patient is in the tub, for unless hyperemia takes place the overheated blood will only be driven in instead of being cooled at the surface In a study of forty-four cases of severe heat stroke during a short severe heat wave in Cincinnati in 1938, Ferris *et al.* found ice water tubbing with massage the most satisfactory first method of approach.

(c) Injection of 1000 cc. or more of ice water into the rectum This method is very little employed in the large clinics where many of these cases are seen each summer in civilian life; Morton's objection to the ice enema is that it deprives one of the use of the rectal thermometer and is also theoretically likely to increase shock

(d) Rubbing the body with ice, or placing the patient in sheets wrung out of ice water These methods are considered much less satisfactory than any of the above; indeed, Elkins, reviewing the subject in 1938, went so far as to say that ice water baths, ice water enemas and packs should never be used

Recurrence of heat stroke is by no means uncommon. Morton found the use of magnesium sulfate enemas to relieve headache in convalescence of considerable benefit, particularly in those patients whose cerebration was slowed and in whom there was no evidence of dehydration He warned that if the patient has been treated in an air-conditioned ward transition from it to an ordinary ward should be a very gradual one. It is the consensus that at least three weeks should elapse before a patient is allowed to travel or to resume activity, and in many instances in military practice it has been found necessary to transfer the soldier to a cooler climate in order to effect recovery.

THERMOGENIC ANHIDROSIS

Wolkin *et al* (1944) described an interesting syndrome seen by them in [illegible]

symptoms were associated with or preceded by a cessation of sweating in each case, which in turn was often preceded by a distinct period of profuse perspiration from a few days up to several weeks duration. The loss of sweating was limited uniformly to the body region below the neck in pronounced [illegible]

the most part remained normal orally except when the external environ-

mental temperature reached heights of 120° F. (48 8° C.) or over; under these conditions there were complaints of extreme feeling of heat, discomfort and irritability. Ladell *et al.* (1944), describing a series of similar cases seen in Iraq, noted in most instances the added symptom of polyuria. The cases described by Allen and O'Brien (1944) in North Australia and New Guinea were also apparently of this same general order. Sulzberger *et al.* (1946), as the result of a thorough study of a typical case of thermogenic anhidrosis seen on Guam, felt that probably ordinary prickly heat and this malady are different manifestations of the same fundamental process in which the horny occlusion of sweat ducts and their orifices appears to play a significant role.

THERAPY

It was found that the only successful management of these cases was to effect their immediate removal from the excessively warm region. The use of salt solution was not found to be of value. It was stressed that these individuals should avoid exposure to excessive heat until the sweat function has returned to normal; indeed, Wolkin *et al.* were inclined to oppose a return to similar climatic conditions even then

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HEAT CRAMPS

(Stokers' Cramps)

This is a type of heat exhaustion seen frequently in those who labor in the heat of firerooms, in deep mines, etc. Following a period of muscular twitching, the patient is seized with violent cramps principally of the abdominal groups; sometimes, however, the spasm is so general as to resemble an epileptic attack The patient is nauseated, dizzy, stuporous, and usually pallid and perspiring, the pulse is rapid but strong and the temperature little if at all above normal. Urine is scanty and there is usually great thirst. These [illegible] the fact that in the excessive ingestion of

[illegible]

clear Loss of vitamins in the sweat is insignificant with the possible exception of *nicotinic acid (niacin).*

THERAPY

The sufferer must be removed to the coolest place available and be allowed complete rest. The opiates are almost completely ineffective in lessening the cramp or pain, but rest alone suffices in most instances. Talbott (1935), reviewing the literature, his experience with Michelsen during the construction of Hoover Dam, and his own observations in the Youngstown mills, [illegible]

salt tablets are given by mouth every hour until [illegible] the patient is put on an exclusive diet of milk, in large quantities, for twenty-four hours.

Prevention consists merely in the ingestion of sufficient salt, though the mistaken idea that dextrose is protective is apparently widespread. Salt may

be taken in the form of a 15-grain (1 gm.) tablet each time water is drunk. Most workmen object to swallowing the tablets, however. Talbott stated that the best way of supplying salt is to place it in the drinking water in a concentration of 0.1 per cent; such a solution may be made by dissolving about 15 grains of sodium chloride in a quart of water (1 gm. per liter). This solution does not have a perceptible saline taste and allays rather than promotes the sensation of thirst. MacLean (1943), describing his experience on a British cruiser during War II, said that ten times this much salt (a teaspoonful to the pint of water) was found to make quite a palatable drink provided the water was ice cold.

All classes of individuals subject to heat cramps by the nature of their occupations themselves realize that the better their general physical condition the less likely they are to develop this syndrome.

THE ANEMIAS

So much progress has been made in hematology in recent years that the hallowed separation of all anemias into "primary" and "secondary" types has had to be superseded by more rational classifications. Undoubtedly the most useful of these for scientific purposes approaches the subject from the standpoint of the size and color of the erythrocyte as indicative of the pathogenesis of each of the maladies; but I doubt if such a classification has as yet been perfected to the point of being of greatest therapeutic service. Therefore in this chapter I am considering the several anemias according to an arrangement designed to facilitate and expedite their satisfactory treatment.

ANEMIAS PRIMARILY BENEFITED BY IRON THERAPY

Nutritional Anemia of Infants.—The normal infant, born into the world with many more erythrocytes and much more hemoglobin than is needed for extra-uterine life, rapidly and proportionately loses both (icterus neonatorum often evidencing the destruction that is going on) for about six weeks, and more slowly to about the tenth week, after which the values slowly rise again to the fifth or sixth month. This period of "physiologic" anemia usually requires no treatment, but the abnormal condition of the blood frequently seen in infants between six months and two and one-half years does call for the institution of therapy. It is a true anemia in which, though the erythrocyte count may be high, low, or normal, the cells are smaller than normal (microcytosis) and are subnormal in hemoglobin content (hypochromia), and there is a *low hemoglobin content of the whole blood.* Enlargement of liver, spleen and lymph nodes, and slight edema of the extremities, are sometimes seen, but the youngster usually appears to be *in a good state of general nutrition; pallor is of frequent occurrence* but alone does not necessarily indicate the presence of this type of anemia. Gastric acidity is sometimes decreased. The low iron content of human and ... sible for the malady, which will appear (a) if the amount ... n sufficient ... the mother ... r (c) if the infant is one of twins or is born prematurely.

Nutritional Anemia of Wartime.—In Britain, Mackay *et al.* (1942), Sinclair (1942), and Davidson *et al.* (1943) offered some evidence of a general lowering of hemoglobin valu ... ted it to a dietary deficiency of iron. ... d opinion were not entirely in accord ... refore the matter of this alleged occurrence of wartime iron *deficiency is controversial.* In the most recent report of Davidson *et al.* (1944) marked improvement in the situation was noted.

Chlorosis.—This disease, *usually* thought to have quite generally disap-

peared, has the following characteristics: (a) occurrence practically exclusively in girls of the servant class between puberty and twenty-five years of age; (b) anemia characterized by moderate or perhaps no reduction in the number

(c) greenish pallor, most marked about the eyes and chin, (d) the usual signs of severe anemia, such as breathlessness, irritability, and edema of the extremities, and often, in these cases, puffiness of the face, (e) constipation and

often irreg-

was not so

ized that a large number of these girls certainly had peptic ulcer or tuberculosis Very interestingly, Patek and Heath (1936) stated that chlorosis has not disappeared, reporting four cases that had entered their clinic in the preceding two years; Olef (1937) was also able to report three cases recently seen. Patek and Heath defined the malady as merely the exaggeration of a normal tendency toward anemia in adolescent girls, created by the increased demand for iron made by growth and by menstrual or other blood loss, and by a diet deficient in iron-containing foods, and they reminded us that Stockman very soundly pointed out these things as long ago as 1895.

Idiopathic Hypochromic Anemia.—This entity has been recently described under a variety of names achylic chloranemia, simple achlorhydric anemia, idiopathic hypochromemia, hypochromic anemia with achlorhydria, primary hypochromic anemia, chronic chlorosis Most of the patients are women between the ages of thirty and fifty years, though the disease is not unknown in men; Thomson (1943) reported nine cases of what seemed to be idiopathic

vitamin B deficiency complexes, paresthesias and other nervous changes (if

murmurs over the whole precordium and perhaps some degree of cardiac dilatation, pallor, chronic fatigue, a blood picture practically indistinguishable from that of chlorosis, and a history which reveals the symptoms to be of long standing

Fowler and Barer (1937) concluded that this is usually a chronic hemorrhagic anemia due to menstrual blood loss and an improper absorption of

disturbances, hypothyroidism, multiple pregnancy, menorrhagia and other forms of bleeding, they classified 24 per cent of their patients as constitutional psychopathic inferiors Lundholm (1939), in an extensive study of the subject in Sweden, recognized hemorrhage as important in the development of this anemia but was unable to correlate the amount of blood lost at menstruation

with the degree *of anemia; very interestingly*, however, he felt that there is an hereditary factor concerned in the etiology.

Anemia of Gastro-intestinal Surgery.—The majority of the cases of anemia [illegible]

[illegible]

hemoglobin content returns to normal in a healthy person after a single severe hemorrhage varies widely with individuals, but in perhaps most instances cell return is completed in four to six weeks with pigment return in six to eight weeks. Neither iron nor liver administration is indicated in these cases ordinarily; the presence of chronic infection *will considerably* retard recovery. Patients chronically bleeding oftentimes present the picture of a severe hypochromic-microcytic anemia—the type in which iron, but *not liver, is strongly indicated.*

Anemia of Pregnancy.—Pregnancy may of course supervene upon any of the anemic states, and in itself may be responsible for anemia following hemorrhage or incident to toxemia or sepsis; but excluding these things, there are anemias of quite other causation. One of these is seen with such *regularity that it has come to be called the "physiologic anemia" of pregnancy:* a steady decrease in both erythrocytes and hemoglobin to about the end of the second trimester Increasing knowledge of blood volume changes has now shown this to be only a reflection of hydremia—dilution of the blood causes it to appear poor in cells and hemoglobin The true (and they are often severe) anemias were shown by Strauss and Castle, in 1932, and by others since, to be almost always of the hypochromic type described above and to occur as the result of a direct dietary deficiency or a deficiency consequent upon impaired gastric secretion. Dieckmann *(1945)* said that in their large experience at the Chicago Lying-in Hospital it had been found that 12 per cent of pregnant women are anemic even as judged by the standards for pregr [illegible] Rarely the anemia is of [illegible] *unde* [illegible]

Hookworm Anemia.—In the anemia consequent upon ancylostoma infestation, which is really an anemia due to chronic blood loss, the erythrocytes are markedly reduced in number and in *size: hemoglobin is diminished* to an even greater extent proportionately. This is, then, a hypochromic-microcytic anemia such as the others already discussed, and it improves quickly and regularly on iron medication without any additional treatment and even before deworming, indeed, this anemia is not often seen in other*wise healthy and well-nourished in*dividuals. Heilig and Visweswar (1942) pointed out that when quick response to iron therapy is not obtained in these anemias, the other infectious diseases which patients in regions of heavy hookworm infestation are likely to have—*malaria, and the like—should* be tre [illegible] tration of the iron.

[illegible] .ia in India have been concerned with the tropical [illegible] mia to be later considered in this article, but Hynes *et al.* (1946) have shown that there also *exists among the poorer classes* in India a type of anemia that is principally normocytic and normochromic, to which neither hookworm nor any of the other tropical maladies seem to be contributory, that is associated with malnutrition, and that responds only *partially to an adequate* dietary but

completely to the same with the addition of iron therapy. This is a very puzzling anemia since it seems to have been adequately established by earlier workers that even the poorest Indian diets contain adequate amounts of iron, and since the patients who were benefited by iron for the most part did not have a typical iron deficiency anemia It seems to me that much work needs still to be done to establish the fact that these anemias are not due to hookworm infestation in the presence of malnutrition, despite the fact that in the study of Hynes *et al* this did not seem to be the case.

THE ADMINISTRATION OF IRON

It seems that the upper part of the small intestine is the chief site of iron absorption and that the soluble ferrous salts are the most easily absorbed and assimilated; indeed it is probable that all other forms of iron must be reduced to the ferrous state before their utilization becomes possible. The nuclei of erythroblasts in the bone marrow take up the iron conveyed thither in the blood plasma; when hemoglobin has been formed from it the nuclei are extruded and the "mature," non-nucleated, hemoglobin-bearing erythrocytes pass into the circulation Under the influence of iron there is an increased rate of delivery of erythrocytes from the marrow for a time, and even reticulocytes—the last stage before full maturity—enter the blood stream; in the early stages of iron therapy the reticulocyte count affords an index of the patient's response to treatment It is usually felt that average hemoglobin regeneration occurs at the rate of 1 to 2 per cent per day, the height of the effect being reached between the twenty-fifth and fortieth days. But dosage must be correct, for there is a definite "threshold" which must be passed before response is obtained. All the signs and symptoms of anemia may be caused to disappear, but the ability to secrete hydrochloric acid will rarely be restored if it has been completely absent. When iron is subsequently omitted the patient is extremely likely to relapse no matter how large an amount of the metal has been stored It would seem that this sequestered iron constitutes, in the words of Witts (1936), "a frozen credit which they cannot liquefy."

Choice of Preparation.—Although iron salts sometimes cause gastro-intestinal irritation, and a few patients respond to iron medication with skin eruptions, general intoxication from the administration of iron by mouth practically does not occur, I have seen only Hurst's (1931) report of one case, Thomson's (1947) one case, and Forbes' (1947) two cases, the latter

the latter, as well as patients on whom a cholostomy or ileostomy has been performed, sometimes do not tolerate it well. Effective doses cannot be given parenterally without incurring the great risk of a severe reaction. We shall therefore consider only preparations for peroral administration, and of these only those most favored by leading students of anemia (Table 23). It is best in using any of them to begin with small doses and take several days to work up to full doses, thus lessening the likelihood of gastro-intestinal upset

Ferrous Sulfate.—The careful studies of Moore *et al.* (1944), and Hahn *et al* (1945), having proved what had long been suspected upon an empirical basis, that ferrous is absorbed much more readily than ferric iron, this would seem to be the most desirable preparation to use, it is certainly the least

TABLE 23.—IRON SALTS FOR ADMINISTRATION BY MOUTH

Salt.	Daily dosage.		
	Adult	Children	Infants to 4 yrs
Ferrous sulfate	12 grains (0.8 gm.) or more	10–12 grains (0.6–0.8 gm.)	6–8 grains (0.4–0.5 gm.)
Reduced iron	45 " (3.0 ")	..	....
Ferrous carbonate (Blaud's pill)	60 " (4.0 ")	..	..
Ferric ammonium citrate	90 " (6.0 ")	60–90 grains (4–6 gm.)	15–45 grains (1–3 gm.)
Ferric pyrophosphate		..	2½ grains (0.15 gm.)

likely of all the salts to cause gastro-intestinal irritation especially if given just after meals. The usual practice is to have one dose taken after each meal and one on retiring. Ferrous sulfate oxidizes to the less effective ferric compound when exposed to air, but the 3-grain (0.2 gm.) coated commercial tablet is stable. Mackay and Jacob (1937) found that the salt keeps more than two months at room temperature if mixed in solution with dextrose and a small amount of hypophosphorous acid; the following prescription may be written for an infant.

℞ Ferrous sulfate	ʒiss	6.0
Dilute hypophosphorous acid (U.S.P. IX)	♏xv	1.0
Dextrose	℥ij	60.0
Chloroform water to make	℥viij	250.0

Dissolve the dextrose and ferrous sulfate in separate portions of chloroform water, then add the acid to the dextrose portion. Mix the two portions and make up to volume with chloroform water.

Label: 1 teaspoonful four times daily in water, milk, or fruit juice. (The teaspoonful will contain 1½ grains, 0.1 gm.)

There is also commercially available an elixir of ferrous sulfate; Reznikoff (1944) said that the adult should be built up to a dose of three teaspoonfuls (about 12 cc.) three times daily after meals. It is best not to use iron in solution in treating adults as it may stain the teeth even though taken through a tube; however, the discoloration is superficial and may be removed by thorough "cleaning" of the teeth by a dentist.

Ferrous Gluconate.—Reznikoff (1944) said that most of the few individuals who are intolerant to ferrous sulfate can take ferrous gluconate in fairly adequate amounts. He starts with one 5-grain (0.3 gm.) tablet after each meal and increases this gradually until the patient is receiving nine tablets a day unless gastro-intestinal symptoms occur.

Reduced Iron.—This drug is insoluble and must therefore be given in capsule form; it can be suspended, of course, but the offering of such a forbidding dose to the patient is inexcusable, of course for infants one can prescribe any of the iron salts in capsules and then empty the contents of a capsule into orange juice which is well stirred while being drunk. Any older child or adult can easily swallow a capsule containing 7½ grains (0.5 gm.) of reduced iron. The average adult dose would require the taking of 6 such

capsules during the day. Warrant for the contention that this preparation is best taken before meals would be difficult to produce, I think, for so many of these patients are achlorhydric.

Pill of Ferrous Carbonate (*Blaud's Pill*).—The coated pills nowadays obtainable keep well enough, but they tend to become very hard and doubt-

the gastro-intestinal tract, but the patient must take 60 pills daily in order to receive full adult dosage

Ferric Ammonium Citrate.—This salt must be given in high dosage and gastro-intestinal irritation from it is not unusual. It is very soluble and may well be prescribed as follows for the adult who would require the average full dose:

℞	Ferric ammonium citrate (powdered)	ʒij	60.0
	Syrup of cinnamon (N.F.) to make	℥viij	250.0

Label: 2 teaspoonfuls in water, milk, or fruit juice three times daily. (The teaspoonful will contain 15 grains, 1 gm., of the iron salt.)

This preparation is perhaps more likely to stain the teeth, even though taken through a tube, than is the solution of ferrous sulfate. Ferric ammonium citrate may also be prescribed in capsules, one of convenient size will hold 4 grains (0.25 gm.).

Ferric Pyrophosphate.—Elvehjem *et al.* (1937) used this preparation satisfactorily in infants; it seems to have the advantages of being quite soluble, practically tasteless and not astringent. A prescription employing it will be found below.

Potentiation of Iron with Copper, Acid, Liver, Vitamins and Other Substances.—Convincing evidence has not been offered that the addition of copper to iron therapy is of any value in the iron-deficiency anemias of adults; indeed, Fowler and Barer (1941) seem positively to have shown that it is

do not feel, however, that copper is of value under any circumstances. A few men think that copper ingestion may incline individuals toward the development of hemochromatosis, but they are probably wrong. An amount of copper sulfate that will give 1/20 grain (3 mg.) to the dose—3 grains (0.18 gm.) added to any of the preceding 8-ounce (250 cc.) prescriptions—may be used, or the following prescription, modeled upon the solution used by Elvehjem, may be written:

℞	Ferric pyrophosphate	℥iss	10.0
	Copper sulfate	gr. iij	0.18
	Alcohol	ʒiij	12.0
	Cinnamon water to make	℥viij	250.0

Label: 1 teaspoonful *daily* in milk or fruit juice.

There have been some indications that other elements, particularly manganese, germanium, cobalt and calcium, and also the substance chlorophyll, have some influence upon iron utilization, but as yet no practical applications that are convincing have been offered. The study of Patek and Minot (1934) *suggested that in certain cases of* iron-deficiency anemia in adults there may be also a deficiency in some useful material contained in bile pigment; but I have heard nothing further of this.

Since iron seems to be either better absorbed from an acid than from an alkaline medium, or is absorbed in a more readily available form, and since many patients with one or other type of iron-deficiency anemia are also deficient in gastric acid, the assumption is quite naturally made that hydrochloric acid should be administered as in the treatment of hypochlorhydria *per se* The fact of the matter is, however, that no clinical study has ever convincingly shown that such therapy has value from the standpoint of increasing the effective utilization of iron, the latest study of this nature that I have seen (Pohle and Heath, 1939) indicated that neither acid nor alkaline salts in large amounts affected the utilization of iron. In some instances acid may undoubtedly help allay the dyspeptic symptoms which frequently afflict these patients, but it may also aggravate these symptoms.

Patients with the iron-deficiency anemias do not ordinarily profit by the addition to the iron regimen of the liver and stomach preparations used in pernicious anemia, or of the so-called "secondary anemia liver extract." Damashek (1945) stated unequivocally that liver has no effect whatever even of an additive type However, it should be remarked that Hartfall's (1934) study of postgastrectomy and gastro-enterostomy anemias indicated that it may sometimes be profitable to consider these cases as partaking of the fea-

thirty-two patients with hypochromic anemia in whom nicotinic acid (niacin)

degree account for the alleged increase in

the daily administration of 25 to 100 mg of ascorbic acid did not raise the hemoglobin levels in their study of iron-deficiency anemias in school children.

Dietetics.—Nowadays, infants are got onto solid foods much more rapidly than used to be the case; in addition to supplying muscle- and bone-building substances, and vitamins, the well-rounded dietary of today's youngsters also keeps pace with the need *for iron*. But as a matter of fact we do not know just which foods are the best from the latter standpoint. Of course elaborate tables of the iron content of foods are available, but studies in recent years have shown that the iron content of a food and the availability of that iron for hemoglobin production are often quite different things. It will require much

laborious work still before we shall be able to say precisely that this or that [illegible]

benefited in the least by an "iron-rich" diet taken for a long time, but the bone marrow responded rapidly and excellently when large doses of iron were added Likewise the study of Brokaw *et al.* (1942) showed that the early introduction of cereals, vegetables and eggs had no marked effect on the hemoglobin level or the red blood count of infants

Routine Administration of Iron in Pregnancy.—A number of modern studies have been increasingly indicating the advisability of the routine employment of iron after the middle of pregnancy, that of Bethell *et al.* (1939) is a recent example Not all obstetricians agree on the point, however, for some, like Labate (1939), believe that since only 50 per cent of women develop anemia during pregnancy it is sounder practice to check the blood status several times during the period and give iron only when indicated. Nevertheless, the evidence of Corrigan and Strauss (1936) in favor of routine use of iron seemed rather convincing One hundred members of a group of 200 normal pregnant women were given iron, the alternate 100 being used as controls; observations began when the women were from three to seven months pregnant, the average one hundred and sixty-two days There were no important dietary or blood-level differences between the two groups Determinations one week postpartum revealed that in the treated group (a) the hemoglobin average was 85 per cent (a gain of 12 per cent over their average in the beginning); (b) none of the women had a hemoglobin below 70 per cent, (c) the erythrocyte count had risen from 3 72 to 4 28 million per cubic millimeter. In the untreated control group. (a) the hemoglobin average was 75 per cent (just what it had been at the beginning); (b) 24 per cent had a hemoglobin below 70 per cent, (c) the erythrocyte count had risen from 3 88 to only 3 94 million per cubic millimeter

Neary (1946) reported that a specially prepared molybdenized ferrous sulfate seemed more effective in the iron deficiency anemias of pregnancy than orthodox ferrous sulfate, but much work will have to be done to establish the superiority of this compound

Routine Administration of Iron in Infancy.—Mackay, in England, is well known as a champion of the opinion that routine iron therapy in the latter months of pregnancy is not enough, and that, at least in the inhabitants of an impoverished area, routine dosing of infants with iron is also urgently needed. Here and there voices are in agreement with her, but nothing [illegible]

hemoglobin level of school children was often below normal and that the administration of even such small amounts of iron as represented in 3 grains (0.2 gm) of ferrous sulfate once daily for five days a week could produce a significant rise in the hemoglobin levels One is certainly unwarranted, however, in drawing the conclusion from this observation that the routine administration of iron to children in the school years is a necessary or advisable procedure.

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Dieckmann (1945) said that he does not see the responses to adequate iron intake postpartum in anemic pregnant women that occur in the normal or in the *nonanemic pregnant* woman, and he therefore feels that a patient who has a hemoglobin of less than 10 gm per 100 cc. at delivery should be watched very carefully to prevent excessive blood loss and that the preliminary preparation for transfusion should be made; if the hemoglobin is less than 9, his patients are transfused either before or *directly after delivery.*

ANEMIAS PRIMARILY BENEFITED BY LIVER-STOMACH THERAPY

Pernicious Anemia.—Pernicious anemia is a chronic deficiency disease which progresses, usually ... the *patient adequately with* ... own economy has failed to p ... of the disease can be held in *abeyance apparently for an indefinite period of* time. The outstanding feature of the disease is the peculiar macrocytic-hyperchromic anemia, accompanied by thrombocytopenia and the appearance of numerous many-lobed polymorphonuclear cells, though there is usually an absolute leukopenia and neutropenia. The number of red cells is usually below 2,000,000, counts of 500,000 or less not being unusual. Hemoglobin is somewhat reduced but not in proportion to the reduction in the number of red cells; consequently there is always a color index higher than one. In addition, there is marked anisocytosis with macrocytes predominating, marked *poikilocytosis, and diffuse and punctate polychromatophilia.* A variety of nucleated red cells, and occasionally mitosis, are seen (Warning: gastro-intestinal carcinoma can give a blood picture astonishingly like this!) In the beginning of a remission there is an increased number of reticulated red cells. The findings of Dameshek and Valentine (1937), and of Stasney and Pizzolato (1942), showed that the changes in the marrow are accurately *portrayed by this picture of arrested maturation* and *malformation* presented in the peripheral circulation. The van den Bergh (indirect) reaction *is* increased. Very interestingly, Warner and Owen (1942) found that patients in relapse frequently show considerable decrease in plasma prothrombin, this hypoprothrombinemia not responding to the administration of vitamin K.

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... complaint of languor, muscular weakness and shortness
... n the beginning,
... *not infrequently*
becomes ... cteristic lemon-
yellow tint to the skin *is seen less often than a simple* pallor. A heart murmur of the "hemic" type is almost the rule, and symptoms of angina pectoris are *sometimes* quite prominent. Slight puffiness of the ankles is a frequent

finding; in rare cases the edema is much greater. Carter and Traut (1943) found some type of cardiovascular manifestation in 257 of their 300 cases. Fever, or the opposite, a *subnormal temperature, may characterize a severe* relapse. And then there are, in addition, the gastro-intestinal and central nervous system symptoms. The former may at one time or another include all the dyspepsias, with periods of diarrhea or apparent gallbladder disturbance being especially prone to occur; tongue and stomach findings are the

[illegible] particularly around

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cases, with extremely rare exceptions, there is a constant achylia—indeed Askey (1944), after reviewing forty-seven reported cases of supposed perni-

with a reemphasis of the fact that pernicious anemia is a disease of the gastric mucosa as well as a disorder of the hematologic and neurologic systems and that treatment sufficient for the maintenance of a normal blood picture may not be adequate to prevent the atrophic changes in the gastric mucosa.

Kaplan and Rigler (1945), in pointing out that statistics unequivocally indicate an etiologic relationship between pernicious anemia and carcinoma of the stomach, emphasized the advisability of examining pernicious anemia patients frequently to detect the onset of gastric malignancy.

This type of anemia occurs among rich and poor alike, among urban and rural dwellers regardless of type of occupation. Only a few cases have been reported in infancy, childhood and adolescence, and the malady is very rare between twenty and thirty, but after this latter age the incidence increases rapidly up to the age of seventy, and then again it is rare in extreme old age; in the eighty cases studied by Hardgrove *et al* (1944) the highest incidence occurred in the seventh decade although the extremes in the series were thirty-seven and eighty-three years. There has come to be more than a suspicion of familial and hereditary tendencies. In the United States, England and France, more men are affected than women, but in Germany, Finland and Scandinavia the reverse seems to be true. Classical addisonian pernicious anemia is very rare in the tropics Most of those who have this disease are of the fair-haired and blue-eyed type; the incidence is well known to *be very low in the full-blooded Negro, and according to Askey (1944) it is* also very low in Chinese and Japanese.

cases of pernicious anemia in
rect diagnosis had been made
t of the cases, that in 53 per
cent the diagnosis had not been made by the first physician consulted, and that in 86 per cent it was not adequately established until hospitalization occurred.

There was little significant advance in the treatment of pernicious anemia from the time that Addison described the disease in 1855 until Minot and Murphy, in 1926, announced that liver contains a principle which stimulates
blood regene ... whose work was based
directly upor ... his associates,
who worked ... arly followed
by remission ... r therapeutic
agents. They first reported forty-five cases, but later brought the number up to 105 cases. Since that time the *mortality rate for pernicious* anemia has declined so uniformly in every age group that there cannot be the least doubt of the specific efficacy of the therapy. Full explanation for this magic is not yet at hand, but the classical studies of Castle and his associates have demonstrated almost beyond doubt that pernicious anemia is a deficiency
... intrinsic factor present in normal
this disease. It is considered
ract with an extrinsic factor

pernicious anemia in
individuals when giver
brain tissue, in which it is apparently stored. *Meulengracht's* (1939) work suggested but by no means proved that the intrinsic factor may be secreted by

The practical discovery, made by Sturgis and Isaacs in 1929, that hog's stomach desiccated and defatted and taken by mouth can replace liver with equal *effectiveness, has been borne out by the experience of physicians throughout* the world. It is believed that the intrinsic substance postulated by Castle exists in an enzyme-like form in the stomach tissue and that it acts on the

patient.

Miscellaneous Macrocytic Anemias of Adults.—Israels and Wilkinson (1936) described four cases of hyperchromic-megalocytic anemia characterized by normal or almost normal gastric acidity, little disturbance of the gastrointestinal tract, no involvement of the central nervous system, and lack of, or poor response to, antianemia therapy. To this syndrome, which they considered a new entity, they applied the title "achrestic anemia." Wauchope and Leslie-Smith (1938) reported a similar case, but it seems to me that much time and exhaustive study will be required to show that this separate classification is warranted. Schwartz and Legere (1943) reported a small series of atypical cases in most of which the symptomatology bore a striking similarity to that of subacute bacterial endocarditis, fortunately they did not set this up as a new subtype of pernicious anemia. Alsted (1939) reported a patient subsisting on a near-starvation diet in whom pernicious anemia is alleged to have arisen from lack of the extrinsic factor only, the patient of Townsend and Begor (1942), who lived on a protein-poor diet for twenty years, seems also to come in this class—indeed, Moore *et al.* (1944) felt that the macrocytic anemia occurring in some patients with pellagra or other vitamin B complex deficiency states is in many instances associated with a dietary deficiency of extrinsic factor plus poor absorption from the intestinal tract; they felt also, however, that inadequate production of intrinsic factor probably contributes to the forming of the picture

Macrocytic Anemias of Infants.—Zuelzer and Ogden (1946) published a detailed study of twenty-five infants having a macrocytic type of anemia of a temporary nature that they believe often escapes recognition. They designated the entity "megaloblastic anemia" because, while the findings in the peripheral blood are strikingly similar to those of addisonian pernicious anemia, they are not constant though a study of the bone marrow permits the diagnosis reliably to be made. They felt that the maturation defect is identical with that in classical perni

deficiency is not a perman

cases of this type respond

earlier literature contained several isolated reports of similar cases, also instances such as those reported by Bass (1944) and Perkins (1944) in which the

anemia except that cord symptoms are not often seen and free hydrochloric acid is often present in the stomach. The response to liver therapy in these

cases is frequently very slow and sometimes blood transfusions are needed to carry the patient through the *pregnancy*. *Wolff and Limarzi (1945)* pointed out that the finding in these cases of a normocytic or microcytic and hypochromic anemia may be misleading unless the bone marrow is examined and

tional severity, six of them continuing to be refractory to liver therapy for a month or longer. The results obtained by Watson and Castle (1945) in three cases indicated the desirability of a therapeutic trial of *orally administered liver extract in these macrocytic anemias* of pregnancy refractory to parenterally administered extract. The present consensus is that dietary deficiency underlies these anemias (though Wiener's, 1944, hypothetical association of this entity with erythroblastosis fetalis is interesting). In 1946, Watson and Castle said they felt their cases were probably due to a deficiency in the same factor that Wills had shown to be missing in tropical nutritional macrocytic anemia (see below).

Tropical (Nutritional) Macrocytic Anemia and Dimorphic Anemia.—Since 1930, Wills and her associates have been studying a very interesting type of anemia in India. Morphologically it seems fairly closely to resemble addisonian pernicious anemia, but differs from the classical entity *principally in not being* associated with achlorhydria or increased serum bilirubin (indirect van den Bergh), and in manifesting no evidences of nervous system involvement. Previously thought to occur predominantly, if not exclusively, in late pregnancy, it is now believed to occur very frequently in males also, though pregnancy does seem to predispose to an attack; the late autumn and winter rise in incidence of cases is as yet unexplained. China, the west coast of Africa, and I ... later apparently but Trowell (1940–

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ciency disease, but whether the missing element is merely Castle's extrinsic

that the Macedonian cases do respond to purified extracts, but more recently Fairley (1940) reported that the dose *must* be *prohibitively* high; Trowell (1943) also found high dosage necessary and, like Wills and Evans, preferred to use the crude extract. Therapeutic response is also obtained to an autolyzed liver extract known as marmite (vegex in the United States), with which cure can be obtained in very few cases of true pernicious anemia. Wills has shown that the active principle in this preparation is not any part of the vitamin B complex but is a substance that is water-soluble, heat-stable in acid medium, and not precipitated or inactivated by 80 per cent alcohol. Watson and Castle's (1946) thorough study of their patient indicated that the active principle in Wills' factor is not identical with folic acid.

I ... instances iron deficiency anemia and the type of macrocytic anemia

...nt and the resulting picture is a very

...d the name "dimorphic anemia" for

this combination. It is not at all unlikely that many instances of this type of anemia will be reported from the Continent as an aftermath of War II.

Sprue.—The typical anemia of sprue is of the macrocytic-hyperchromic "pernicious" sort and responds to liver therapy and apparently also to folic acid; the matter is discussed in detail under Sprue.

Infestation with Diphyllobothrium Latum.—In some instances of infestation with the fish tapeworm there arises an anemia closely resembling that of the true addisonian pernicious anemia; this matter is discussed under Tapeworm.

Anemia of Hepatic Disease.—Wintrobe's (1936) studies conclusively showed that in cases of hepatic disease, except when there is a complicating infection or loss of blood, the anemia is morphologically very similar to that of pernicious anemia. Achlorhydria is not the rule, however, nor are there often any evidences of cord damage. Wintrobe concluded that the anemia is very likely due solely to the inability of the liver to store the hematopoietic principle; the studies of Goldhamer *et al.* (1934), and of Rosenberg (1936) support this hypothesis. This anemia due to hepatic damage may be controlled at times by the injection of liver extract.

Anemias Associated with Gastro-Intestinal Pathology and Surgery.—There have been some reports of one or another form of chronic dysentery, and also ulcerative colitis, associated with anemias morphologically similar to the true pernicious type; injections of liver extract in these cases can be expected to [illegible]

tomoses; Barker and Hummel (1939), however, suggested the possibility that the anemia occurring in conjunction with strictures and anastomoses may be a distinct disease entity.

ADMINISTRATION OF LIVER AND STOMACH PREPARATIONS

At the present time throughout the world intramuscular injection of liver extract has practically entirely replaced other methods of liver therapy for the following reasons: (1) Greater efficacy; patients in whom it is not possible to reach a completely normal erythrocyte count with oral methods of therapy can in most instances be brought up to normal by injection, since uneven [illegible]

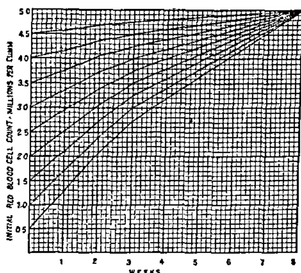
mouth. (2) Acceptability; as compared with the oral administration of liver or stomach preparations daily, the intramuscular injections three or four times *weekly in the beginning and only once weekly, or even less often,* thereafter, are greatly preferred by practically all patients. Since the freeing of the preparations from histamine, the anaphylactic shock type of reaction is now extremely rarely seen; the injection is usually not followed by excessive pain. (3) Travel; a patient can be intensively treated by injection before [illegible]

can be had for the money when it is purchased as extract for injection, though of course patients who cannot learn to inject themselves after a while will necessarily have frequently to meet the physician's fee. (5) Speed; the patient

in dire need in a severe relapse can be stimulated more quickly by injection than by oral administration *in most instances. Liver extract is available in* vials in solution for intramuscular injection in both "crude" and "refined" forms. The intravenous injection of liver extract is so frequently provocative of severe reactions that it is practically never resorted to nowadays.

Dosage of Liver Extract Intramuscularly.—This matter really comprises the three separate subjects that follow herewith:

Criteria for Guidance in Dosage.—There are no absolute ones really, since patients vary in response and the available commercial *preparations are* widely different in strength, with differences of as much as 2 cc. in dosage between them in order to obtain comparable results. The only safe plan is to use a reliable, clinically tested extract in dosage recommended by the manufacturer and to vary that dosage, especially not fearing to increase it, according to the reaction as indicated by frequent blood studies. Beginning



The red blood cell count, at weekly intervals, for each initial red blood cell count after liver extract therapy, intramuscularly. Example: With an initial red blood cell count of 1 million per cubic millimeter the count at the end of one week will be 1 7 million, at two weeks 2 4 million, at fifteen days 2 5 million, and so on

two to ten days after therapy is started the reticulocytes rise to a major peak within three to ten days, the height of which peak is inversely proportional to the level of the red cells, other things being equal. The mature red cells require some time to begin reaching the peripheral blood stream in full numbers, but usually in about two months *the red cell count is within* normal limits (Wintrobe, 1933: average for men, 5,400,000; for women, 4,800,000)—where it should be the aim of therapy to keep it thereafter. Riddle's (1940) *study of the data on* 523 patients indicated that neither the reticulocyte nor the erythrocyte response is superior for the purpose of estimating the effectiveness of treatment, but since the erythrocyte count is certainly the one most often employed, I am reproducing here with Dr. Raphael Isaacs' kind permission his chart of the erythrocyte response that may be expected in adequately treated cases

A Dosage Plan.—The several leaders in the study of pernicious anemia

have been employing the products of different manufacturers and hence their dosages have differed but I think it will best serve the reader's purpose if I present here the plan of only one of these groups, namely Strauss and his associates in Boston, who have for many years been employing the Solution Liver Extract Crude-Lilly in the strength which contains 1 U.S.P. unit to the cubic centimeter. This extract, not being highly purified, contains many other substances present in liver besides the hematopoietically active material for pernicious anemia; this was formerly held to be an advantage, but nowadays it is generally recognized that refined liver extract is fully as satisfactory a preparation on all counts as the crude extract. In commencing the management of a previously untreated patient, Strauss *et al.* inject 10 cc. every three or four days during the first two or three weeks; thereafter weekly injections of the same amount are given for the remainder of the first year. If the results have been satisfactory with regard to every aspect of the disease during the year, they feel that the 10 cc. injections may then be given once in only two weeks, adequate maintenance requiring the injection of a dose at intervals of one to four weeks depending on the individual case. Weekly dosage must be at once resumed upon the reappearance of any manifestation of the disease. They have had cases in which more than 20 cc. weekly were necessary to arrest the progress of the spinal cord lesions; especially resistant are cases complicated by infection or arteriosclerosis.

Massive Dosage.—Strauss and Pohle (1940) concluded as the result of treating each of twelve patients in relapse with 160 cc. of Solution Liver Extract Crude-Lilly intramuscularly during a period of one week that the majority of patients cannot be satisfactorily treated by the use of massive injections at long intervals Askey (1941), upon the other hand, found that the use of an initial large dose of 10 to 20 cc of Solution Liver Extract Purified-Lilly ("purified" extracts contain 5, 10, or 15 units per cc. against 1 or 2 units per cc for the "crude") enabled him to obtain satisfactory control in sixteen of nineteen patients who were thereafter given maintenance injections at only monthly intervals Schwartz and Legere (1944) felt, as a result of eighty-eight relapses due to self-neglect in fifty-four individuals, that accurate evaluation of the results of massive dose therapy is unlikely because of the difficulty of making sufficient adjustment for the highly individualized behavior of patients with pernicious anemia during remissions

Reactions to Intramuscular Liver Injections.—One might almost say that severe systemic reactions to these intramuscular injections do not occur, yet very occasionally a patient does develop peripheral circulatory collapse very suddenly and apparently unaccountably, though Reznikoff (1940) reported one instance in their clinic in which they were reasonably certain that the material had entered a small blood vessel. Asthmatic, urticarial, gastro-intestinal and other allergic reactions do occur, however, Schwartz and Legere (1946) reported sensitivity reactions to the parenteral administration of liver extract in 17 per cent of 396 patients According to Feinberg *et al.* (1943) cutaneous and intracutaneous tests indicate that the specificity of this reaction is related to a special fraction of liver not bound with the ordinary protein fraction but associated with the antianemic fraction Bauer *et al.* (1947) reported fourteen cases of acquired sensitivity to a pork liver extract given intramuscularly, the symptoms of sensitivity being abolished by change to an extract derived from beef liver. In these cases clinical experience consistent —and skin tests to some extent—indicated that the sensitivity to liver extra

represented an acquired type of species rather than organ-specificity. Upon

[illegible]

acid with dramatic and satisfactory response, though in order to obtain maximum effects, stomach and iron were added to supplement folic acid. The folic acid was given in a dosage of 60 mg. per day, later reduced to 30, and finally to 20 mg. per day. Delikat (1943) reported desensitization in one case in which the beginning dose of liver was 0.1 cc. which was increased by the same quantity at each successive dose given every second day until a dose of 1 cc. was reached; thereafter an increment of 0.2 cc. was used; after reaching 3 cc. the dose was increased by 0.5 cc. at two weekly intervals until 4 cc. could be given in a single injection, the patient thereafter tolerating this dose every four to five weeks. Another of Delikat's patients attended the clinic every six weeks and received her requirement of liver extract in divided doses, starting with 0.1 cc. with increments of 0.1 cc. at intervals of twenty minutes until the first signs of intolerance appeared; after the slight reaction passed away she went home and returned on the following day, at which time dosage was started at the level reached on the previous day and proceeded at increments of 0.2 cc. at twenty-minute intervals; in this patient the full requirement of 4 cc. for six weeks was usually injected thus in two days. Schwartz and Legere (1946) reported the successful desensitization of ten of eleven patients, in whom all other methods of reestablishing adequate levels of parenteral liver therapy had failed, by the concomitant employment of "antigen H," a compound prepared on the hapamine principle (see Section on Allergy). Of course when none of these methods succeeds these patients have to be treated by liver or stomach preparations by mouth.

Results of Liver Extract Therapy.—It is simplest to consider this subject under the following heads:

Objective Changes.—Usually the skin begins to acquire color in the first week and later becomes healthy and moist in appearance. The mucous membranes share in this improvement and the tongue returns to normal in most instances; persistent tongue lesions are felt by some observers to be associated with marked cord involvement. Isaacs, Sturgis and Smith advise painting the lesions with 1 to 2 per cent silver nitrate. Hemic murmurs, anginal symptoms, spleen palpability and edema disappear; though it should be remarked that if the patient has much cord involvement and has been

and marked. Appetite, physical strength and sexual power return. The distressing gastro-intestinal symptoms disappear, though if there has been normal bowel activity looseness may supervene for a short time. Dizziness, blurred vision, headache, dyspnea disappear.

stand or those with nearly complete loss of voluntary control of the lower extremities, especially if this is of acute onset and of less than one or two months' duration, may recover to such degree that only minimal neurologic

cerebral and mental symptoms appear

months may be required to

perversion of the sense of

smell will be completely cured in from two to four months; (e) muscular

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distally unless the impairment had already reached the point of cutaneous anesthesia, in which latter cases some degree of permanent sensory blunting with troublesome paresthesias may be expected; (g) the loss of the vibratory *sense is least likely to be completely overcome, though patients with ataxic* symptoms up to several weeks of duration will usually improve under treat-

neurologic defects resulting from disease of the lateral columns of the cord, carry the poorest prognosis of all, though extensor plantar reflexes presumably *of short duration not infrequently revert to normal after treatment is begun* but when symptoms have been present for longer than one or two months the

the point very strongly that pernicious anemia is unfortunately too infrequently diagnosed in its early stages by physicians because they are not sufficiently on the *qui vive* for "atypical" cases, the fact being, however, that these atypical cases are often really typical since the lingual, anemic and neurologic manifestations frequently occur independently of each other; even in individual patients undergoing successive relapses of the disease lingual or anemic changes may predominate on one occasion and neurologic involvement on

observation of the therapeutic response to liver extract is a practical method of proving the diagnosis in cases of neurologic involvement in which the other evidences of pernicious anemia are not presented in a clear-cut fashion

Effect on Childbearing—*Pregnancy used to be looked upon as a calamity* in the life of a woman with pernicious anemia, but women are now carried through safely to the birth of healthy babies.

Effect on the Dangers of Surgery.—Apparently patients on liver therapy tolerate operations very well upon the whole and are good surgical risks, but Hahn (1934), reviewing thirty-two cases, stated his strong impression that surgical procedures definitely *tend to precipitate or increase* neurologic symptoms; he recommended intensification of treatment both before and after operation.

Effect on the Gastric Acidity.—A few cases have been reported in which there was a return of free hydrochloric acid after adequate liver therapy, but Goldhamer (1937), reviewing the subject, doubted that these were cases of true pernicious anemia. He did find, however, that the intrinsic factor is present in the gastric juice in induced remission

Liver Extract Preparations for Oral Administration.—Liver extract in powder form is available in vials of 4.25 gm equivalent to one-third the U S.P. oral unit, the daily dosage being at least three such vials; capsules of the extract are also available containing one-fiftieth U.S.P. oral unit, or one-ninth U.S.P. oral unit, daily dosage of the latter preparation being nine capsules. Liquid liver extract for oral use is available commercially in eight-ounce and one-pint bottles, the daily dosage being 45 to 60 cc. dependent upon the preparation employed

Hog Stomach Preparations for Oral Administration.—Dried and powdered defatted hog stomach tissue is available in a preparation known as Ventriculin *in bottles of 100 and 500 gm., the daily dose being four heaping tablespoonfuls* taken in divided doses in water, milk or fruit juice. Another preparation obtained by incubating liver with minced hog stomach is known as Extralin; it is available in bottles of 84 and 500 capsules, the daily dose being three to four capsules three times daily.

Fresh Liver by Mouth.—It is now generally agreed that the amount of fresh liver required to induce remission and maintain health in the average adult uncomplicated case of pernicious anemia is 200 to 400 gm (approximately ½ to 1 pound) net weight daily It may be taken either raw or lightly cooked, provided the water employed in cooking is added to the completed

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which does away with the trouble of "lightly" cooking and also makes it possible to use the tough, fibrous, and hence cheaper cow's liver. The cachets must be filled just before using else they become soggy and *liable to come* apart in the mouth. Kidneys are about one-half, sweetbreads and brains about one-third as valuable in treatment as liver The liver may be eaten at one or be divided between all the meals of the day. Farquharson and Graham (1930) found a broth made from beef or pork liver to be inexpensive,

... follows: 500 gm. of liver

all the juice.

t jar, shaken

rs, if possible

after cooling

sufficiently is strained through cheesecloth by twisting round and round, as much fluid is expressed as possible and the total amount of fluid obtained is given to the patient every day. It may be taken cold or hot, and various flavoring agents—onions, soup powders, tomatoes—may be added if desired. Davis *et al.* (1943) described a method for the production of a palatable and

readily assimilable whole-liver preparation by means of enzyme digestion of raw liver with papain; but the process was too laborious and complex for employment in the home and a preparation of this "proteolysed liver" is not as yet commercially available

Resistance to Liver Therapy.—In their original paper, Minot and Murphy indicated that infection could inhibit the effectiveness of the therapy, an observation substantiated in many subsequent reports. Moosnick *et al.* (1945) said that sudden failure of a patient to respond to adequate amounts of liver extract in the absence of factors known to interfere with therapeutic response has been observed by them and reported to them in a few instances in recent years In one such patient, in whom it was assumed that anti-pernicious anemia factor could be stored in but not effectively elaborated by the liver, since biopsied liver and bone marrow tissue both showed fatty metamorphosis, the progressive anemic state was brought into complete remission by means of the administration of a 5 per cent solution of choline chloride, 20 cc intravenously at the rate of 1 cc per minute daily for sixteen days. The patient expired from intercurrent pneumonia while in remission and therefore no further studies of the case were possible

OTHER THERAPEUTIC MEASURES

Folic Acid.—The historical background of this agent is discussed in Sprue (*q v*) In 1945, Spies *et al* reported that a group of anemias including pernicious anemia, megaloblastic anemia of infancy, and some cases of nutritional macrocytic anemia occurring with poor diets alone or in association with sprue, pellagra, chronic alcoholism, carcinoma of the stomach or pregnancy, responded approximately as well hematopoietically to folic acid as to liver extract Goldsmith (1946) obtained good hematological responses to folic acid in four patients with nutritional macrocytic anemia with a dietary history indicating deficiency of vitamin B complex In the "megaloblastic anemia" of infants described by Zuelzer and Ogden (1946), it was found that the response to folic acid was indistinguishable from that to liver extract; beginning between the third and fourth day the reticulocytes in the blood began to rise and shortly afterward the hemoglobin level and the red blood count began to improve The bone marrow also assumed a normal pattern within a few days. However, though the conjugases in liver principle may produce folic acid by effecting its release from the conjugated form in which it appears in foods, folic acid does not effect relief in any anemia that will not also be relieved by liver extract Furthermore, folic acid is not the principle in liver extract effective in pernicious anemia, it is neither the extrinsic nor the intrinsic factor of Castle, and it does not restore the [illegible]

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hematologic response, he found that an occasional patient responds as rapidly to folic acid as to treatment with liver but that the majority respond hematologically more slowly The response of three of his fourteen patients was very slow and hematologic remissions could not be induced with folic acid despite administration of fairly large doses; however, in all three patients satisfactory remissions were induced by intensive employment of liver. And as regards the effect upon neurologic complications in pernicious anemia, there can be no doubt of the failure of folic acid as indicated in the reports

of Vilter *et al.* (1947), Hall (1947), Heinle and Welch (1947), Meyer (1947), and others. Vilter *et al.* of Spies' group in Cincinnati, found that doses of 10 to 50 mg. daily did not prevent the development of neurologic complications in four persons and that after these complications had developed it did not stop their progression, even in dosage of 100 to 500 mg. daily; liver extract did, however, promote rapid improvement. In Hall's series of fourteen patients treated for many months with folic acid at the Mayo Clinic, ten instances of peripheral neuropathy were observed before institution of treatment; *in these ten patients* improvement occurred in four, temporary improvement followed by relapse in four, and no improvement in two. In the two instances of subacute combined degeneration of the cord observed before institution of treatment, evidence of progression was noted during administration of folic acid In the cases in which symptoms or signs of neurologic involvement did not exist prior to institution of treatment with folic acid, two instances of paresthesia and three of early signs of combined sclerosis occurred while treatment was being given, neurologic manifestations developing in some cases despite induction of satisfactory hematologic remissions.

It would seem obvious that the substitution of folic acid for liver in the treatment of pernicious anemia is extremely hazardous in view of the above. It has been claimed for folic acid that one of its great advantages is that it may be taken by mouth, but I think most physicians will doubt the value of this since patients so quickly escape from control when they are permitted
urged for folic acid is that
principle—Frommeyer
nded it in such cases;
but this too is a doubtful advantage since in most such instances switching brands of extract, or changing from pork to beef extract, suffices to effec control of the anemia.

Meyer (1947) reported that in five patients *folic acid in doses of 5 to 10* mg. orally daily, combined with 1/2 unit of liver extract intramuscularly
than that anticipated from adequate
e in a position to do clinical experi-
point. According to Heinle (1946),
existent even with dosage much
to 150 mg at a single dose,
ction has precipitated *shock*-

patients on a restricted dietary
rge doses of vitamin C (ascorbic
acid) permitted a response to liver extract therapy otherwise unattainable. In early 1947, Dr. Dyke kindly informed me that subsequent observations confirmed to him and his group the correctness of their original observation; it is now their practice in the initiation of liver treatment in pernicious anemia to give 50 mg. of ascorbic acid three times daily routinely for the first two weeks. They have furthermore observed that, under the conditions currently prevailing in England, many patients who are on maintenance treatment with liver require ascorbic acid during the spring, the vitamin C reserves from the previous summer and autumn appearing to suffice only to carry them through the winter. Cayer *et al.* (1946), studying the vitamin levels of eight patients with pernicious anemia here in the United States, found levels of vitamin A and carotene and vitamin C essentially normal,

but the levels of niacin, thiamine and riboflavin were below normal. They felt that the results of their study would justify the administration of B-complex vitamins to pernicious anemia patients if liver extract alone fails to produce a satisfactory response.

Blood Transfusion.—Davidson *et al.* (1946), of Castle's group, have shown that the maturation arrest in bone marrow characteristic of pernicious anemia can be caused to disappear temporarily through the artificial decrease in the degree of bone marrow anoxia effected by the transfusion of blood. But it was also shown in their study that transfusions, however helpful they may be in emergencies, cannot be looked upon as accomplishing the same thing as the injection of liver extract (or of folic acid insofar as the hematologic responses alone are concerned), since in the transfused patient the leukocyte and platelet counts do not rise as they do when liver extract or folic acid is administered. Since 1940 the use of red cell residues that are by-products of plasma production, resuspended up to the original volume in physiologic saline, has been increasingly practiced; in 1944, Cooksey and Horwitz were able to report on 15,000 such transfusions in the city of Detroit alone. Murray *et al.* (1943), Alt *et al* (1944), and Cooksey and Horwitz (1944) specifically mentioned the use of red cell transfusions satisfactorily in pernicious anemia. Since there is practically universal testimony to a lowered incidence of transfusion reactions when red cell suspensions are employed instead of whole blood, I should think that this new method would be highly advantageous in view of the pernicious anemia patient's penchant for developing reactions. However, since we are no longer processing large amounts of plasma in this country, I do not know where the red cells are to come from.

Iron and Hydrochloric Acid.—It is believed that in pernicious anemia the breakdown products of the red cells are stored in the body and are available at once for the manufacture of hemoglobin should normal blood formation occur as the result of a natural remission or of treatment with one of the new specifics However, in a few cases the amount stored may not be sufficiently great to prevent the color index from falling to and remaining below 1.0 for a considerable period as the red cells continue to rise; undoubtedly there are instances in which the employment of iron is helpful, but these cases are certainly not frequently encountered. The routine employment of iron in pernicious anemia is unjustified.

Since the overthrow of the intestinal contamination theory of the etiology of pernicious anemia by the newer studies which have shown the disease to belong among the disorders of deficiency, there seems little rationale for the employment of hydrochloric acid However, a number of physicians continue to prescribe it in doses of $\frac{1}{2}$ to 2 drachms (2–8 cc), well diluted and taken as a routine with meals, finding that flatulence and diarrhea that are not alleviated by specific therapy are kept well in check by the addition of this measure.

ANEMIAS PRIMARILY BENEFITED BY CORRECTING AN UNDERLYING DEFICIENCY

Vitamin Deficiencies.—Anemia does not characteristically occur in the states due to *vitamin deficiency* of one sort or another, and when seen it is nearly always of the hypochromic-microcytic type caused by insufficient intake of iron and is correctable by the administration of *iron together with the vitamin* that has been ingested in insufficient quantity. A rather constant *exception*, however, is scurvy, in which anemia is so regularly seen as practically to constitute one of the invariable signs. It is usually of the hypochromic type but may occasionally resemble the pernicious group *at least in its morphologic characteristics*, achylia and cord symptoms of course not being present. This anemia is rapidly corrected by the administration of vitamin C as in Scurvy. The macrocytic anemia of pellagra is discussed under the miscellaneous macrocytic anemias in the section on Anemias Primarily Benefited by Liver-Stomach Therapy.

Thyroid Deficiency.—Anemia is a not infrequent finding in cretinism and myxedema, though it is not actually demonstrable so often as the pallor would lead one to expect. Usually of the hypochromic (iron deficiency) type, it may also at times have hyperchromic (pernicious) characteristics; particularly is the latter true in myxedematous individuals in whom, according to Lerman and Means (1932), the incidence of achlorhydria is high. Both iron and liver, depending upon which is indicated by the morphologic characteristics of the anemia, will induce bone marrow responses in these cases, but it seems undeniable that thyroid substance alone will slowly accomplish the same thing Supplementing thyroid administration with one or other of the hematopoietic agents therefore seems the ideal therapy. In an elderly man with chronic untreated myxedema and an associated hyperchromic macrocytic anemia in whom four months of treatment with thyroid, liver extract and iron apparently did not influence the anemia, Glass (1943) reported that he obtained prompt and complete erythropoietic response when testosterone was used in addition.

ANEMIAS PRIMARILY BENEFITED BY COMBATING BLOOD LOSS

This matter is treated as one of the types of iron-deficiency anemia in the earlier part of this chapter.

ANEMIAS PRIMARILY BENEFITED BY COMBATING THE UNDERLYING INFECTIONS

In sepsis, which is the most *frequent cause of severe* acute anemia of infectious origin in the temperate zones, transfusion is not often employed in these days of specific chemotherapy. Malarial anemia, whether severe or [illegible]

other infectious diseases more rarely—is followed by [illegible] chronic hemolytic jaundice; in these instances curing the infection does not

always cure the anemia Anemia often results from the paroxysmal hemoglobinuria that occurs occasionally in syphilis; specific antisyphilitic treatment may not entirely abolish the *in vitro* evidences of hemolysis, according to Castle and Minot (1930), but it usually causes disappearance of the clinical manifestations.

In states of chronic infection such as empyema, endocarditis, osteomyelitis, tuberculosis, rheumatic and focal infections, a "low-grade" microcytic and slightly hypochromic anemia often appears, occasionally there are evidences of bone marrow depression A recent study by Cartwright *et al.* (1946), of Wintrobe's group, of the utilization of iron in these anemias showed that there did not result a significant increase in the iron content of plasma despite the fact that the plasma iron values of the patients were consistently much lower than normal. These workers were therefore led to speculate to the effect that perhaps the failure in the utilization of iron for hemoglobin regeneration during chronic infection is due to some unknown, persistent and urgent demand for iron to fulfill a function in relation to infection.

ANEMIAS PRIMARILY BENEFITED BY COMBATING CHEMICAL POISONING

A few chemical substances administered as drugs, and a larger number with which many individuals are obliged to come into contact in this industrial age, are capable of considerably depressing the hematopoietic system Those which are of principal concern to the man in general practice are discussed elsewhere in the book (see the chapter on Poisoning, and the Index); for a consideration of the others the reader will be obliged to consult specialized works on industrial toxicology.

ANEMIAS PRIMARILY BENEFITED BY SPLENECTOMY

Congenital hemolytic anemia (icterus) is the classical entity in which splenectomy almost invariably arrests progress The disease occurs on a familial background of the same malady and is characterized by relatively mild jaundice (which is accentuated at times of increased hemolysis), by enlargement of the spleen, chronic anemia with many erythrocytes that are microcytic and spheroidal, reticulocytosis out of proportion to the reduction in erythrocytes, increased fragility of the erythrocytes in hypotonic saline solution, and increased urobilin in the blood In the presence of this typical picture, splenectomy will apparently quickly and permanently put a stop to the hemolysis, though the spheroidicity of the cells persists Whether the concept of an acquired form of hemolytic anemia of this type is admissible is at present controversial. Many observers feel that such cases are really only latent stages of the congenital disease which are diagnosed when they have become activated by some infectious, toxic, or metabolic disturbance In a discussion in which he championed the acquired form as being a separate entity, Fowler (1941) nevertheless pointed out that a diagnosis of this form is not infrequently made embarrassing by the subsequent appearance of case histories or of active cases in the patient's family. The especially interested

reader will likely find the review of Dameshek and Schwartz (1940) very stimulating. Of the 106 cases reported in the literature at the time they wrote, transfusions were given in sixty-six and were unsuccessful in arresting the disease in twenty-two instances; splenectomy induced arrest in twenty of the twenty-three cases in which it was performed. A recent very interesting case reported by Dameshek and Levine (1943) indicated that repeated transfusions in cases of acute hemolytic anemia may be followed by isoimmunization and the development of irreversible hemolysis; as a result of this, splenectomy—which might originally have been curative—may prove ineffective. Dameshek and Schwartz considered Lederer's anemia as almost certainly the same thing as acute hemolytic anemia, and most hematologists seem now to be in agreement that this is so.

ANEMIAS PRIMARILY BENEFITED BY TRANSFUSION WITH Rh NEGATIVE BLOOD

(Erythroblastosis Fetalis and Certain Transfusion Reactions)

In 1940, Landsteiner and Wiener discovered the existence in man of a new blood group factor, designated the Rh factor, that is inherited as a Mendelian dominant just as are the previously well-known factors, A, B, AB and O. Since the original discovery the further studies of Wiener and Levine and their respective groups have shown that there are eight subtypes of the Rh factor; but the fact of chief clinical importance is that there is a certain small proportion of individuals who do not have this Rh factor in their blood—according to Diamond (1945), about 13 per cent of the white population is Rh negative, 10 per cent of the Negro population is negative, and 1 per cent of the Chinese and American Indians are negative. Waller and Levine (1944) also found an extremely low incidence of Rh negativity in a small group of Japanese studied. The significance of Rh negativity may be expressed as follows: (a) the Rh factor exists in the red blood cells of Rh+ persons and is an antigenic substance; (b) the blood does not contain agglutinins (antibodies) against this Rh factor; (c) when the blood of an Rh+ person is introduced into the circulation of an *Rh−* person, *agglutinins against the Rh* factor will be developed in the blood of the Rh− person, or the blood of an Rh+ fetus in the uterus of an Rh− mother may under certain circumstances provoke *the same response in the mother's blood,* (d) if, then, upon a subsequent occasion the Rh− person is again the recipient of Rh+ blood there will occur a violent reaction between this blood and the agglutinins *that were built up in the Rh−* blood by the preceding administration of Rh+ blood, or if an Rh+ fetus is again implanted in the uterus its red blood cells may be destroyed by these agglutinins. For the highly specialized investigator the subject of the Rh factor has become immensely complex in recent years with the piling up of new discoveries, but for the solving of ... still suffices ... viduals as ... time still ... h limited ... specialists ... lve a diffi-

in the field whenever tests with ...

cult problem To be sure, it is now known that an Rh positive individual may become sensitized and develop immune bodies against an Rh agglutinogen, but these cases occur with such extreme rarity that they need not concern most practitioners and they certainly cannot be taken into account in this present article. Two types of antibodies specific for the same Rh subgroup—agglutinating antibodies and blocking antibodies—may be provoked to appear in the blood of an Rh− person; both signify sensitization of the individual to the Rh factor, but the clinical importance and the relative significance of agglutinating antibodies in contrast to blocking antibodies have not been fully established.

In 1944, Kracke and Platt very graphically presented the possibilities of Rh reactions in the terms of four typical cases seen by them at the Emory University Hospital. It seems to me still that the subject may be most simply presented in terms of these four cases

Case 1 was a two-day-old infant of an Rh+ father and an Rh− mother. The father had transmitted the Rh+ factor to the fetus, the fetus had passed

performed by Howard *et al* (1947), of the University of California Medical School, it was determined that Rh− women who bear Rh− infants show practically no agglutinins or blocking antibodies in their serums at any time, those who bear normal Rh+ infants show demonstrable antibodies only after parturition, those who bear Rh+ infants afflicted with subclinical hemolytic disease of the newborn show significant rise in titers of Rh agglutinins or blocking antibodies beginning about ten weeks antepartum, reaching a maximum level at the second week postpartum, and then disappearing; those who bear Rh+ infants with frank erythroblastosis fetalis show high titers early in pregnancy, which tend to drop gradually as pregnancy progresses, *i e.*, the agglutinin titer drops as the blocking antibody titer rises. Howard *et al* stressed the importance of testing for Rh antibodies in Rh− women regardless of parity because the receipt of possible Rh+ blood through transfusion may have occurred in the distant past and been forgotten. They also felt that an occasional woman may be so easily immunized that she is capable of developing antibodies of sufficient intensity to harm the fetus during the first pregnancy, but with regard to this point Levine (1946) said he did not know of any case of fetal death due to erythroblastasis fetalis in the first pregnancy of an Rh− woman who had not been previously immunized by intravenous or intramuscular administration of blood

The following procedures were recommended to the Staff of Columbia Hospital here in Milwaukee early in 1947 as a practical means of detecting and handling the Rh factor situation in the vast majority of pregnant women. (1) Have mother Rh tested on first visit to office, if she is Rh+ no further tests are necessary. (2) If she is Rh− the husband must be tested; if he is Rh− no further tests are necessary (3) If husband is Rh+ (and wife is Rh−), anti-Rh determinations should be performed on the mother's serum at the end of six months, if she is a primipara and has no Rh antibodies at that time no further tests are necessary. (4) If she is a multipara and has no Rh antibodies at six months the probabilities are that sensitization has not

occurred; however, she should again be tested within a few days of the expected date of confinement, and if this last examination is negative the infant is unlikely to develop erythroblastosis. (5) If the six months test is positive, the titer of antibodies should be determined and a repeat titration should be performed at the end of the eighth month; an increased titer at this time is serious.

It is not superficially apparent why the incidence of erythroblastosis fetalis is only about 0.1 to 0.2 per cent of births. The following reasons have been proposed by investigators in this field, some of them substantiated by actual findings and others mere speculation: (a) variations in the permeability of the placenta may effect the passage of Rh+ factor and anti-Rh agglutinins between mother and fetus; (b) more than one pregnancy may often be required to induce an adequate degree of immunization of the mother, the modern tendency to restrict the number of children therefore working against a high incidence of erythroblastosis; (c) mild and unrecognized forms of the disease may occur, (d) heterozygous fathers, *i.e.*, those who have inherited the Rh factor from only one parent, transmit the factor to only some of their children and of course the children who do not inherit it escape erythroblastosis. Potter (1944) described twins one of whom died of erythroblastosis and the other remained normal, the affected twin and the father being Rh+ and the normal twin and the mother Rh−. She contended that the father was heterozygous for the Rh factor and that two ova were fertilized, one by a sperm carrying an Rh+ gene and the other by a sperm carrying an Rh−. The mother had been sensitized to the Rh factor either in a previous pregnancy when an Rh+ fetus had been carried or possibly during the course of this pregnancy by the Rh+ twin. The antibodies produced in the mother passed through the placentas of both fetuses but affected only the one that was Rh+. The study of Race *et al.* (1943) showed that about 57 per cent of Rh+ males are heterozygous. The studies of both Hunt (1947) and Falls (1947) strongly indicated the propriety of encouraging Rh− women with Rh+ husbands to become pregnant in the belief that they have not much more than the ordinary risk to run from abortion.

Case 2 was that of a twenty-five-year-old primipara who was delivered of a normal infant but who was given a blood transfusion because of severe hemorrhage as the result of a lateral rupture of the placenta sustained during delivery. She experienced an immediate severe reaction and examination of her blood revealed that she was Rh−. In this case her Rh+ infant had immunized her against Rh+ blood but for some reason her antibodies had not traveled back through the placenta to the infant; the infant therefore escaped erythroblastosis fetalis but when the mother was subsequently given the transfusion of Rh+ blood she herself experienced the reaction.

Case 3 was that of a fifty-eight-year-old patient with an established diagnosis of aplastic anemia. She had received numerous transfusions before entering the hospital, but careful questioning elicited that the first two transfusions were uneventful while each succeeding one had produced a more severe reaction. This patient was found to be Rh− and demonstrated the production of anti-Rh agglutins in an Rh− patient by means of multiple transfusions of Rh+ blood

Case 4 was that of a forty-year-old-female admitted eight months postpartum with a diagnosis of Banti's syndrome. It was decided to remove the spleen and by way of preparation for her operation to give her two or more

blood transfusions; but because of her recent pregnancy it was decided to test her for Rh factor. She was found to be Rh− and in addition to have a quite enormously high titer of anti-Rh agglutinins in her blood, which presumably resulted from her last pregnancy. The experience of Young and Kariher (1945) with two patients indicated that sensitivity to the Rh factor, once it is acquired, may persist for many years and probably for life, in their cases they proved retention of sensitivity nearly eight and sixteen years respectively.

THERAPY

Transfusion of Rh− Individuals.—The observations of Hattersley (1947), confirming earlier workers, indicated that there is probably ample reason for believing that every Rh− individual is capable of developing Rh antibodies, and that for this reason such persons should always be transfused only with Rh− blood Tisdall (1946) well pointed out the practical point that since there is as a rule no harm in administering Rh− blood to an Rh+ woman, if the Rh status of the patient to be transfused is unknown, Rh− blood should be administered. Levine and Waller (1946) emphasized the importance of transfusing all Rh− female patients even as infants with Rh− blood. According to Wiener (1947), when transfusing an Rh− person only Rh− blood of the type rh (new nomenclature) should be used in order to *avoid reaction in patients sensitized to rh' or rh"*; however, Unger *et al.* (1947), of the large blood transfusion service at the New York Postgraduate Hospital, said that for ordinary hospital work this precaution is of very little consequence

Transfusion of the Erythroblastotic Infant.—Potter (1947) said that while a few investigators have reported finding Rh+ cells satisfactory for purposes of transfusion of infants with erythroblastosis, the idea being that these cells will absorb the excess antibodies, at the present time the evidence supports the use of Rh− cells in all transfusions for the first weeks of life In transfusing the infant one may safely figure on 10 cc. per pound of body weight, the transfusions to be repeated as often as necessary to maintain a level of 10 gm. hemoglobin per 100 cc. and 3,000,000 erythrocytes per cubic millimeter. Wiener and Hyman (1946) said that the mother of an erythroblastotic infant is the ideal donor, it being necessary only that her red cells be washed with saline solution in order to remove the antibody-containing plasma; two washings are sufficient, and since all grouping and matching tests may be omitted when maternal red cells are transfused, this takes even less time than the regular procedure, especially when one must wait long periods for professional donors to appear At the end of the second washing the packed cells may be transfused by adding only a minimal amount of saline to reduce the viscosity, thus permitting a double dose of red cells to be given in the same small volume as a single transfusion. It is said that rarely more than two or three such transfusions are required to effectuate a permanent cure. Wallerstein (1947) said that infants who have progressive icterus despite transfusion procedures and who develop pronounced hepatomegaly and splenomegaly followed by severe toxicity and death, probably come to this end by reason of the fact that the liver is unable to cope with the large quantities of bilirubin and toxic products liberated when all the Rh+ cells are destroyed; such infants die a liver death despite the fact that transfusions may have temporarily replaced all the Rh+ with Rh− cells.

Kernikterus, spasticity, and other afflictions apparently having their origin in Rh incompatibility, do not seem to be averted by transfusion. It is not unusual to find anemia a month or more after the infant's discharge from the hospital; Wallerstein (1947) said that an additional transfusion of 75 to 100 cc. of blood may then be required and that at this time Rh+ blood will suffice.

In the process of "exchange" transfusion, the aim of which is to effect the removal of the Rh+ erythrocytes of the infant before they are destroyed in large numbers by the maternal antibody, the procedure consists in the actual withdrawal of 90 per cent of the infant's blood and its replacement with innocuous Rh− blood; in order to avoid subjecting the child to the dangers of shock from exsanguination, the withdrawal and replacement are carried out simultaneously. Wiener *et al.* (1947) described the treatment of twelve infants in this way; it was said that all but one of the twelve made a spectacular recovery although five were desperately ill when treatment was instituted. Cole (1947) seemed impressed with the potentialities of this method and so too was Potter (1947), though the latter felt that the technical difficulties make it impractical for general use; many surgeons are employing it, however, with good results

Serum Albumin in Erythroblastosis.—Jacobi *et al.* (1946), arguing that the edema in severe cases of erythroblastosis fetalis is not due to anoxemia as is the commonly accepted belief but is rather associated with a lowered osmotic pressure because of low blood protein levels as a result of liver damage, treated two cases empirically with serum albumin with success The amounts of serum albumin used were from 6.25 gm. to 11.25 gm.

Feeding of Erythroblastotic Infants.—On the basis of the demonstration by Witebsky *et al.* (1942) of Rh antibody in breast milk, it would seem inadvisable to permit mothers of infants with erythroblastosis fetalis to supply these infants with breast milk

ANEMIAS FOR WHICH THERE IS NO SATISFACTORY THERAPY

This category embraces the anemias for which no place can be found anywhere in the therapeutic classification which I have been *employing* in this chapter. In the hemolytic entities among them, transfusion sometimes tides [illegible] really the patient over [illegible] The list cannot be effecti[illegible] [illegible]alue of is short: aplastic [illegible] splenectomy are controversial points); Cooley's anemia (familial erythroblastic anemia, target cell anemia, thalassanemia, Mediterranean Disease—the reviews of Smith, 1943, and Dameshek, 1943, are most interesting); leuko-erythroblastic anemia; sickle-cell anemia; anemia of toxic nephritis (see Nephritis); anemias resulting from radium or roentgen ray injury; [illegible] Hodgkin's disease, and carcinomatosis of the bones, [illegible] fava-Micheli's, Gaucher's, Niemann-

BLOOD DISTURBANCES OTHER THAN THE ANEMIAS

ERYTHREMIA

(*Polycythemia Rubra Vera*)

Erythremia is a rare disease occurring in all races, in either sex, and usually after the age of fifty. The cause is unknown but in some of the cases, usually

severe headache, muscular spasms and neuralgias and paresthesias of the extremities. There is a pronounced hemorrhagic tendency in the disease. Examination reveals red cyanosis of the face and hands (though it is said that an occasional patient may be actually pale, but it is doubtful if any victim of this disease is at *all* times pale), a greatly enlarged spleen in the majority of instances, congested conjunctivae and a typical blood picture.

lets are also sometimes much increased, hemoglobin is more than 100 per cent Although the total blood volume is greatly enlarged, the increase in plasma is not in direct proportion to that in cells, with the result that viscosity is much increased. Despite the diffuse capillary dilatation that is known to occur in this

rate sometimes increased. Three types of cutaneous manifestation have been described in association with this entity: a purplish redness of the gums, a papular itchy urticarial eruption with surmounting vesicles or pustules with bloody crusts, and a vesicular eruption simulating dermatitis herpetiformis.

Dameshek and Henstell (1940) felt that erythremia is probably more common, particularly among Jews, than is ordinarily suspected, and that it may masquerade for months or years under such guises as neurasthenia, migraine, cardiovascular-renal disease, gastro-intestinal disorders and peripheral vascular disease. An increased excretion of uric acid in the urine is said to be frequently associated with polycythemia vera. Tinney *et al.*, reporting in

cerebellar hemangioblastomata, both cases apparently recovering upon the removal of the neoplasm. This is a fatal malady but there are remissions in most cases. Death seldom occurs under five years and may be deferred as long as twenty years, though this is unusual, some of the cases of long stand-

ing seem to merge into anemic, leukemic, or thrombocytopenic states. Tinney *et al.* (1945), reviewing 163 cases treated prior to the introduction of radioactive phosphorus, said that in general the prognosis is favorable; however, when anemia becomes severe and the leukemoid reaction becomes so marked that the peripheral blood picture resembles that of myelogenous leukemia, the prognosis is poor. If death is directly attributable to the erythremia, it is consequent upon increased sluggishness of the circulation or due to a vascular catastrophe, such as hemorrhage or thrombosis.

THERAPY

Venesection and Reduced Iron Intake.—*Frequent extensive bloodletting* affords temporary relief in most patients, but a more rational type of therapy seems to be that of Dameshek and Henstell (1940), who aimed at producing a stat[illegible] total blood [illegible] Their metho[illegible] lobin is reduced to 80 or [illegible] ocrit reading to bet[illegible] eight venesections. [illegible] requires avoidance of red meat, meat soups, liver, eggs, rye bread and brown cereals (protein may be derived from fowl once a week, fish twice a week, cheese, milk and legumes). Dameshek (1946) said that during the asymptomatic periods of six to eighteen months induced by this therapy the red cell level gradually rises; the red cell count as an index of therapy is therefore of little value in his opinion. He felt that the hematocrit value is the best index of the patient's status although the hemoglobin concentration alone might be used since this correlates fairly closely with the hematocrit level. Holbrook (1947), of Milwaukee, said he had gained the impression in the study of a series of cases reported in 1941, that repeated venesections may reduce the blood count too rapidly, *i.e.*, if a very high count is brought down several million within a few weeks it is probably undesirable since in doing this one may have reached a point that represents relative anemia in the erythremic patient. No one of course sees a sufficiently large number of patients with erythremia to enable him to settle any very fine points in the therapy.

Potassium Arsenite.—Forkner, Scott and Wu (1933) obtained distinct improvement in all of their six patients by saturating with Fowler's solution in the conventional way except that they liked to reach 20 minims (1.2 cc.) three times daily instead of stopping at 10 minims as is usual in other conditions.

Roentgen Therapy.—Irradiation of the spleen is contraindicated since there are a number of cases on record in which the procedure has increased the severity of the disease; irradiation of the long bones, however, is thought by some observers to be of value. The usual practice is to apply a rather large dose to the long bones, the scapula, the sternum, the pelvis, and eventually [illegible] on the ribs. The effect is temporary, and Minot has said [illegible] becomes ineffective. A considerable, [illegible]se in the leukocytes of the circulating blood indicates that the leukocyte-forming tissue of the bone marrow is being injured and calls for immediate cessation of the treatment. Hunter (1936), following the earlier European observers, believed general irradiation

to be the method of choice; Fitz *et al.* (1942) reported a case apparently

voltage x-ray in these essentially normal individuals because of possible dangers of radiation malignancy or leukemia.

Radioactive Phosphorus.—This agent is produced by the bombardment of ordinary red phosphorus by very rapidly moving deuterons generated in the cyclotron When administered to the patient the agent is quickly concentrated in bone marrow, liver, spleen, bones, etc, in which site its breakdown and decay occur It is said that nearly 50 per cent of any given dose is normally excreted during the first six days and that after six weeks no significant amount of radiation can be found in any tissue following a single administration of radio-phosphorus The agent is given either orally or parenterally and in dosage and at intervals varying according to the hematologic and clinical status and response of the patient The largest series of cases I have seen reported was that of Erf (1946), who said that of twenty-five cases treated seventeen showed satisfactory hematologic and clinical remissions of from six months to three years Rhoads (1946), merely reviewing the subject, said that the patient is enormously relieved, that there is objective evidence of improvement, and that from every point of view in treating this disorder the use of radioactive phosphorus is the method of choice. However, Dameshek (1946) said that he had hesitated to use this potentially dangerous material in an individual with a relatively long life span, since he wondered whether the acute leukemic states that have occurred in some cases are due to the drug or are associated with the erythremia, the data

still a clinical experimental tool

Phenylhydrazine Hydrochloride.—The use of this agent has been abandoned, and indeed it is apparently no longer obtainable in the United States

HODGKIN'S DISEASE

Hodgkin's disease is an affection of the lymph nodes of unknown etiology and invariably fatal termination Males are more frequently affected than females, the majority of cases in either sex occurring between the ages of fifteen and thirty-five. In the usual form of the disease the patient notices a gradual, nonpainful, discrete enlargement of glands in the cervical region; in the beginning the enlargement may be unilateral but both sides are almost invariably involved ultimately In most cases the axillary and then the inguinal glands, and finally both superficial and deep glands all over the body, become involved. Moderate enlargement of the spleen, and often an increase in the size of the liver, takes place. The patient loses weight and becomes cachectic. General pruritus of a very severe and persistent type is a

not infrequent early symptom; very rarely cutaneous lesions of a varieg sort are recorded. A peculiar feature of the disease is the frequent alterna febrile and afebrile periods. The enlargement of cervical, mediastinal, re peritoneal, or mesenteric groups of nodes may cause symptoms which m the picture a very complex one; involvement of the vertebrae and the c when this occurs, is usually a very late manifestation. Initial involvemen the retroperitoneal nodes without subsequent mediastinal or peripheral m festations is infrequent. Hodgkin's disease usually terminates in death wi two to three years, though Jackson and Parker (1946) recorded that of si nine patients in their series, 40 per cent had had the disease for five years or m and an additional 6 per cent for more than ten years. Death is usually to mechanical obstruction of one sort or another or to intercurrent infect

Hodgkin's disease presents with numerous variations; the above ske is of only the most frequently seen type. Histologic examination of an exci node (Meyer, 1941, said that nodes from sites other than the groin are m apt to show affection by the primary disease rather than mere lymphadeni shows very definite alterations in structure which cannot be described h for obvious reasons; likewise, the blood and marrow picture in the vari types of Hodgkin's disease is a topic that is still in a state of too great c fusion to warrant its discussion in a book of this sort. Herbut *et al.* (19 described six cases that at one time during the lives of the patients w

another according to the amount and type of stimulation ...culosis and brucellosis either of these theses h ie first vague account this disease, which was fully described by Thomas Hodgkin in 1832.

THERAPY

General Therapy.—It is felt to be important that the patient carry out regimen as for tuberculosis, with rest and fresh air, moderate exposure sunshine, and a good nutritious diet—"other than that," says Craver, "the is not much to be done." Jackson and Parker (1946) said that the prese ... to go to term provided that or

... rays to the enlarged node ...ently leads to considerabl amelioration of symptoms The effect is always temporary, however, an the response to subsequent courses of treatment is less satisfactory. Finall a point is reached at which there is no response at all. Jackson and Parke (1946), in a thorough review of Hodgkin's disease, said that the most valuabl therapeutic measure is irradiation although there is no consensus concernin the best method of applying it. They said that they were in agreement wit some other observers that under irradiation the duration of life is actuall prolonged and that they have been increasingly impressed with the wisdo of relentless treatment even in the face of what appeared to be overwhelmin odds. Evidence of any consistent beneficial effect from the use of radioactiv

phosphorus is not yet at hand, Hoster *et al.* (1945) treated eleven selected patients without benefit.

Nitrogen Mustards.—The introduction into therapy of these new halogenated alkyl-amines, by-products of research in the war gases, is an extremely interesting departure, but their employment is still entirely in the stage of clinical experimentation and much time is likely to pass before they or derivatives from them or allied substances will possibly become available for the use of the general practitioner. In a review of sixty-seven cases of lymphosarcoma, Hodgkin's disease, leukemia and a limited number of allied miscellaneous disorders treated with these agents by four groups of physicians in as many cities, Goodman *et al.* (1946) stated that salutary results had been obtained particularly in Hodgkin's disease, lymphosarcoma and chronic leukemia, and that indeed in the first two disorders a dramatic improvement had been observed. However, some patients failed to benefit for reasons unknown. In the acute and subacute leukemias varied responses were ob- [illegible]

[illegible]

anemia, it was felt could be largely avoided by adherence to safe dosage schedules However, these optimal dosage schedules, as well as possible combinations of this treatment with radiation or other agents, remained still to be determined. Other series of experimental cases have been reported by Jacobson *et al* (1946), and Alpert and Peterson (1947). In the experience of the latter authors, some of the results in Hodgkin's disease were spectacular, others fairly good and the remainder poor. In the cases showing considerable sensitivity to the drug there was a general tendency for the tumors to recur, an experience which it is said that all other investigators in this field have had. Gilman (1947) stated that resistance to the nitrogen mustards themselves develops and that the response becomes less marked with successive courses of therapy. Craver (1947), reviewing the whole subject of the lymphomas and the leukemias authoritatively, said that neither the nitrogen mustards nor radioactive phosphorus can at the present time supplant x-ray therapy and that they are best regarded as complementary tools, since in most cases situations arise demanding x-ray therapy either as a supplement or alone.

Arsenic.—This old "specific" is used in the same manner as in the treatment of leukemia (*q v.*) The nodes sometimes temporarily recede under arsenic therapy, but it does not seem that this response is obtained nearly so often as it is with irradiation.

Treatment of Anemia.—Jackson and Parker (1946) said that in their opinion transfusions are of inestimable value; they said they had never seen an untoward reaction when the bloods were properly matched in both the major and minor agglutinins Iron is often also of value and perhaps very rarely liver extract.

Surgery.—It is surprising to find Jackson and Parker (1946) expressing the view that when the lymph node enlargement is localized surgical excision should be practiced and the area subsequently irradiated; they admitted, however, that suitable cases are rarely seen and that even in them some hidden focus not apparent at the time of operation may frustrate attempts at cure But they were able to cite two patients who were subjected to radical excision of cervical lymph nodes, one being alive and free from signs and symptoms of the disease ten years after operation and the other seven years after operation. However, it is the opinion of most students of this disease that even the removal of a single gland for purposes of diagnosis should be postponed until it is certain that the procedure is absolutely necessary.

LEUKEMIA

Leukemia is a relatively rare and always fatal disease of unknown etiology, characterized chiefly by the presence in the blood stream of large numbers of abnormal white cells, though in some of the cases there occur at times aleukemic phases in which the white count is found to be below normal Leukemia is a disease of fowls and the lower mammals as well as of man. It occurs more frequently in males than in females; a familial tendency has not been proved.

Acute myelogenous and lymphogenous leukemia occurs usually in children and nearly always, except for the monocytic form, in individuals under twenty-five years of age. It is rapidly fatal, death occurring usually within a few days to a few weeks at most. The attack is often superimposed upon an acute infection, such as tonsillitis or a furuncle. There is malaise, headache, high fever, bone pain, extreme prostration and a rapidly increasing pallor. Ulcerative lesions appear in the mouth and throat, and marked enlargement of the regional lymph nodes of the neck occurs very rapidly; lymph nodes elsewhere in the body, and also the spleen, are slightly enlarged. Bleeding occurs both externally and internally from the mucous membranes and sometimes also in the fundus of the eye; hemorrhages of the skin are almost the rule and various types of vesicular eruptions are frequently seen. There is very rapid decrease in the number of red cells and the amount of hemoglobin, and marked platelet reduction; at the same time the number of white cells is mounting, though it rarely attains the great height seen in the chronic form of the disease. Immature red cells are also present in large numbers. Lymphocytes and lymphoblasts usually constitute more than 90 per cent of the white cells but sometimes myeloblasts predominate, it is only in recent years that the monocytic form of blood picture is being reported, a few cases of acute eosinophilic leukemia have been described. In leukopenic leukemia the cells are similar to those in myelogenous leukemia but the total [illegible] bnormal; in aleukemic myelogenous leukemia [illegible] sent in the peripheral blood but the bone [illegible] anges Whether or not a true basophilic leukemia occurs is a much discussed subject.

Chronic leukemia is insidious in its onset but usually causes death from anemic exhaustion, hemorrhage, or intercurrent infectious disease, for which the resistance is much lowered, in about three years; a few cases last as long as ten years and a rare case even longer, but true recovery never occurs

The most prominent symptoms are marked enlargement of the spleen, which causes great discomfort, pallor, dyspnea, dizziness, palpitation, bone sensitiveness, gastro-intestinal disturbances, loss of weight and progressive weakness. Leukemic infiltration of the skin occurs fairly commonly especially in lymphatic leukemia. Hemorrhage and fever are much later in their appearance than in the acute form of the disease In lymphogenous leukemia the spl

ment c

enous

prolife

is pale in color, with a low red count and much reduced hemoglobin, immature and abnormal red cells are present The white count is rarely increased to more than 200,000 and consists almost exclusively of pathologic lymphocytes; the platelets are always reduced. In the myelogenous type of the disease there is an increase in white cells from 100,000 to 1,000,000 or more, polymorphonuclear, eosinophilic and basophilic leukocytes are relatively and absolutely increased, the lymphocytes are relatively reduced but absolutely increased, and immature cells from the bone marrow are present Blood platelets, usually abnormal in appearance, are initially increased but finally decreased in number Neutrophilic myelocytes usually predominate, but monocytic and eosinophilic cases are seen. A few cases of plasma cell leukemia have been seen, and a series of transitional cases between typical multiple myeloma, which is a leukocytic tumor, and plasma-cell leukemia has been reported. Heller *et al* (1947) presented evidence indicating that the disease known as aleukemic myelosis is fundamentally leukemia Bone marrow changes have been observed to precede the positive leukemic manifestations in the peripheral blood, indicating that bone marrow biopsy might be advisable in all doubtful cases Chronic myelogenous leukemia occurs most often in individuals between twenty-five and forty-five years of age, chronic lymphogenous leukemia in those between forty-five and sixty Leukemia is rare in pregnancy, Cross (1944), reviewing the literature and adding two cases of his own, brought the total number of congenital cases up to twenty-two, according to Erf (1947) there have been no reports of leukemic newborns delivered of leukemic mothers. Leukemia is not hereditary. The absolute incidence of leukemia is difficult to determine because undoubtedly many individuals die undiagnosed, but Sacks and Seeman (1947) stated authoritatively that since 1940 more than 5000 persons have died annually of the leukemias in the United States Henshaw and Hawkins (1944) reported that leukemia was re … frequently among physicians than …lation, and Ulrich (1946) reported … much higher than among other physicians

Leidler and Russell (1945) have stated that neurologic signs and symptoms are present in about a third of the cases of leukemia and that hemorrhage in the brain sufficiently extensive to be the immediate cause of death occurs in approximately 29 per cent of the patients According to Merrill and Jackson (1943), renal failure often occurs in leukemia as a result either of obstructive or infiltrative leukemic lesions, stone, or nonleukemic degenerative disease of the kidneys The very interesting case report of Shorvon (1946) indicated that possibly in very rare instances acute gout can result solely from the increased amount of uric acid in the blood of the leukemic individual

THERAPY

Acute Leukemia.—There is nothing to describe.

Chronic Leukemia.—*Irradiation.*—Radium is sometimes applied over the splenic area but roentgen therapy is the more generally accepted method However, there is certainly still great diversity of opinion with regard to technic, some advocating that attention be directed to the spleen and enlarged nodes only, others irradiating only the chest or trunk, and others practicing "spray" irradiation of the entire body. Craver (1947), reviewing the whole subject of the lymphomas and the leukemias authoritatively, [illegible]

much experience in the treatment of these cases can cite numerous specific instances in which there can be no doubt that irradiation has prolonged life for many years. Results are usually much more satisfactory in myelogenous than in lymphogenous cases.

Radioactive Phosphorus.—See the discussion in Hodgkin's disease.

Radioactive Sodium.—Evans (1947) reported on the use of radioactive sodium, the patient drinking the radioactive element combined as sodium chloride in a solution that is practically tasteless, the general distribution of the sodium throughout the body producing whole body radiation. He said that by giving a treatment every two or three months in two cases of chronic lymphogenous leukemia he had been able to control the condition for approximately a year at the time of his report Fairly good results seem to have been experienced in two out of three cases of myelogenous leukemia

Nitrogen Mustards.—See the discussion in Hodgkin's disease.

Urethane (Ethyl Carbamate).—This drug was given its first trial in the treatment of leukemia by Paterson *et al.* (1946), who noted that a patient with metastatic carcinoma of the breast had developed severe leukopenia while under urethane therapy. These observers reported that urethane causes a great decrease in leukocytes in most cases of leukemia and that clinical remissions comparable to those induced by x-ray therapy occur in chronic myelogenous and chronic lymphatic leukemia. Hirschboeck *et al.* (1947) reported results quite similar to those of Paterson *et al.* The latter observers treated twenty-two cases of leukemia, using the urethane orally in doses of 15 grains (1 gm.) three times daily in 7½ grain (0.5 gm.) capsules, or intramuscularly as a 40 per cent solution in doses of 15 to 30 grains (1 to 2 gm.) three times daily. They reported that the use of enteric-coated capsules eliminates nausea unless large doses are given over a long period of time. The intramuscular injections were painless and local reactions were not observed, but a few patients experienced drowsiness and dizziness following introduction of the drug by this route, which is not surprising since urethane was many years ago employed as a sedative and hypnotic and is still to some extent used as a general anesthetic in animal experimentation; the patients taking the drug by mouth also experienced a sedative effect but it was slight. [illegible] *et al.* had acute or subacute leukemia; [illegible] was accomplished [illegible] brupt and coming usually within the first week of therapy—indeed in four of the cases leukopenia below 1000 was induced. But in spite of this depressing effect on the leukocyte count all of these patients continued along the characteristic

downward course of the disease, though a brief remission was observed in three of them. In chronic lymphatic leukemia, of which they had nine cases, the results were somewhat better, six of the patients responding fairly well but not so precisely and promptly as they would probably have done to x-ray. However, four cases of chronic myelogenous leukemia showed remarkably good response to urethane, a fall in the leukocyte count to normal with maturation of the cells having occurred The spleen and lymph nodes became normal in size in these cases, the anemia was corrected, and the symptoms disappeared, the effect being similar to that of x-ray therapy. In these cases remissions had lasted for from six weeks to longer than eight months at the time of the report.

Of course the place of urethane in the therapy of leukemia cannot be accurately assessed at the present time on the basis of the very slight evidence at hand, but it does seem apparent that little is to be expected of it in the acute leukemias and that in chronic lymphatic leukemia the result of its employment is quite unpredictable. Most consistent success was achieved by Hirschboeck *et al* in chronic myelogenous leukemia, but these observers were unable to conclude that it offers any advantage in this type of the disease over x-ray therapy other than its ease of administration. The agent is also more easily used than the nitrogen mustards or radioactive phosphorus, and since it is perhaps equally as effective in chronic leukemia as these agents its use is probably to be preferred, in the opinion of Hirschboeck *et al* Urethane's effects are apparently at times strikingly similar to those achieved with Fowler's solution. It was thought possible that in the future a program of combined therapy with x-ray, urethane and the nitrogen mustards may be developed as a more effective tool than any one of these therapeutic agents when employed alone, but the authors carefully pointed out that in contemplating the use of urethane one should bear in mind Jaffe's (1947) warning that it has been found to be potentially carcinogenic in animal experimentation.

Myelokentric Acid.—Miller *et al.* (1947) reported the treatment of eight [illegible]

[illegible] liferation. Thirteen partial remissions occurred in these eight patients; all [illegible]

Transfusion.—Transfusion has often been effectively employed to offset the tendency toward hemorrhage and to relieve the anemia temporarily until it has been possible to irradiate the patient sufficiently to produce results. Kirschbaum and Preuss (1943), reviewing 123 fatal cases of leukemia at the Cook County Hospital, said that repeated transfusions of blood had been the most beneficial treatment. It having been reported a good many years ago that following whole blood transfusions some of the myeloblasts in the peripheral blood in acute myelogenous leukemia are replaced by early stages of myelocytes, Schwind (1947) undertook to determine whether the factor causing this partial maturation might reside in the plasma. To this end he gave plasma transfusion to two patients with acute myelogenous leukemia who were in good clinical condition and had no need of whole blood transfusions at the time. The result was that in both of these patients there oc-

curred a partial maturation of the myeloblasts; the substance causing this effect was not found to be present in the gamma globulin fraction of blood plasma or in dried plasma.

Intercurrent Infection.—For many years it has been known that intercurrent infections during the course of leukemia are accompanied by a fall in the number of leukocytes. Some years ago Gamble treated two cases by the therapeutic production of malaria. In each case there was a prompt fall in leukocytes to half the previous number. Following the termination of the paroxysms, however, the leukocytes rose, in three and six days respectively, to approximately their previous level. Lucherini had better results in his case, the leukocytes fell from 250,000 to 4400 after twelve paroxysms, and at the end of the reported observation of the case, six weeks after paroxysms were stopped with quinine, the blood count was: leukocytes, 5800, erythrocytes, 4,400,000, hemoglobin, 52 per cent; the differential count was said to have been normal. Ulrich and Parks (1940) and Heinle and Weir (1944) [illegible]

Arsenic.—In 1931, Forkner and Scott reawakened interest in the use of Fowler's solution by their report of good results. Forkner (1940) stated that he begins with 3 or 4 minims (0 2 to 0.3 cc.) thrice daily in a beverage after meals and gradually increases about a minim a day until 8, 10, or even 15 minims are being taken three times daily. The leukocyte count is said to begin dropping on about the twelfth day with symptomatic remission following shortly. The dose is decreased a minim a day when the leukocyte count is [illegible] 4 or 5 minims three times daily has been acc[illegible] of [illegible] drug must be reduced *slowly* as above stated to accomplish this. Arsenic is much used but not all observers feel that it is often of value; for example, Wintrobe and Hasenbush (1939) found it of no value in a small group of lymphogenous cases and of less value than irradiation in myelogenous cases. In their experience the toxic symptoms following arsenic were greater than those following x-ray. Kandel and LeRoy (1937) found it difficult to judge whether the likelihood of inducing hyperkeratosis, neuritis, herpes zoster, and possibly cirrhosis with arsenic outweighed its beneficial effect in the disease. The organic arsenicals intravenously are definitely dangerous in leukemia; a number of acute deaths have been reported.

AGRANULOCYTOSIS

(Agranulocytic Angina, Malignant Neutropenia, Primary Granulocytopenia)

It does not seem that anyone has fully classified the varieties of agranulocytosis, but the following seem to have attained at least tentative rank as distinctive entities: (a) the low-grade chronic type first described by Roberts and Kracke in 1931, and referred to recently by both Kracke (1947) and Hattersley (1947); (b) the type, either acute or chronic in its course, which seems to be associated with excessive splenic lysis of granulocytes and is apparently corrected by splenectomy—first reported by Wiseman and Doan, in 1939; (c) the unusual "cyclic" cases in which granulocytopenic

episodes, with spontaneous recovery, are alleged to occur at somewhat regular intervals; and (d) the type characterized by acute onset, brief fulminating course, and death in the majority of instances. It is the last of these types only which has been studied sufficiently so that its existence as an entity may be granted without reservation, and it is this type alone with which this present article concerns itself Incidentally, however, one should mention the interesting infectious agranulocytosis of cats, with which several groups of investigators have been working, though it is not known to bear any relationship to the human disease. The onset and course of classical human agranulocytosis are often of dramatic suddenness and dispatch: collapse, chill, fever, red throat or ulcerative stomatitis, and possibly ulcerative (without the usual inflammatory reactions) and gangrenous lesions elsewhere throughout the body; sometimes jaundice; very occasionally a slightly enlarged spleen; marked leukopenia and granulocytopenia without notable anemia; sepsis, stupor and death Though monocytes may sometimes be present in the peripheral blood in abnormally high percentages (Reznikoff, 1938, felt that persistent monocytosis is evidence of good prognosis), the majority of the white cells are usually adult lymphocytes Marked thrombopenia and a consequent bleeding tendency are probably rarely seen in cases of unequivocal primary granulocytopenia. The findings of Fitz-Hugh and Krumbhaar (1932), corroborated by those of Custer (1935) and Darling *et al.* (1936), established the primary fault as a maturation arrest of the myeloid (white cell) series in the bone marrow analogous to the erythroblast arrest in pernicious anemia

This entity was first described by Schultz, in 1922. In the period 1930–1940 the findings of numerous investigators demonstrated that the drug amido- [illegible] organic antimonials, acetphenetidin (phenacetin), dinitrophenol, thiouracil. As long ago as 1931, Pepper suggested that agranulocytosis might be an allergic manifestation, and in 1934, Squier and Madison fully established the fact clinically by showing that it is possible to produce granulocytopenia at will by readministration of amidopyrine to individuals whose primary attack of agranulocytosis had followed use of the drug. The reason that countless individuals are able to take amidopyrine, the sulfonamides or any of the other above-listed agents without developing agranulocytosis is obviously the fact that they are simply not allergic to these compounds.

THERAPY

It seems to be the consensus that death in most instances in agranulocytosis i[illegible]
bacteren[illegible]
that pen[illegible]
on the b[illegible]
life in th[illegible]
penicillin or to deny its apparently fine effectiveness in agranulocytosis, nevertheless it seems to me justifiable to remind the reader that few physicians are yet reporting cases in which they have had the courage to resort to the use of penicillin alone. It is therefore difficult to assess with absolute accuracy the part played by penicillin in the treatment of agranulocytosis

since the therapy so often [illegible]

[illegible]

[illegible]

agent that was the cause of the trouble.

Discontinuance of the Use of the Causative Drug.—*In the case of the* organic arsenicals, the sulfonamides, and indeed most of the other agents that have been convicted in the causative role, it is easy enough to determine whether or not the patient has been taking the drug and to order its discontinuance as a first move in undertaking the treatment of an attack of agranulocytosis. But it is more difficult to be certain with regard to amidopyrine because it is an ingredient in so many "medicines" *sold over-the-counter* in American drug stores. The following is the most complete list that I have been able to obtain of the proprietary preparations that did or do contain amidopyrine, or a compound of it, or that are capable of yielding it in the body in such form as would carry the potentiality of causing agranulocytosis. The list was brought up to date by Kracke, in 1938; from it I have deleted two preparations, "antabs" and "analgia," which the manufacturers claim do not con[illegible] h acetphenetidin is said to have [illegible] to it I have added "causalin" whi[illegible] s been reported in association with attacks of agranulocytosis. The list does not include many of the large group of "patent" or secret formula medicines.

Alphebin	Benzedo compound	Midol
Amarbital	Causalin	Mylin
Amidol	Cibalgin	Neonal compound
Amidomine	Cinchopyrine	Neurodyne
Amido-neonal	Compral	Nod
Amidophen	Cronal	Novaldin (novalgin)
Amidos	Dymen	Optalidon
Amidotal compound	Dysco	Paralga
Amifeine	Eumed	Phenamidal
Aminol	Gardan	Phen-amidol
Am-phen-al	Gynalgos	Phenopyrine
Ampydin	Hexin	Pyramidon
Amytal compound	Ipral-amidopyrine	Pyraminal
Baramid	Kalms	Seeqit
Barb-amid	Lumodrin	Yeast-vite

Penicillin.—The successful employment of penicillin in the control of the septic state while spontaneous recovery [illegible] Sprague and Ferguson (1944), one case [illegible] Smith *et al.* (1944), one case; Russek *e*[illegible] Kauvar (1945), one case; Urbach and Goldburgh (1946), one case; [illegible] and Myers (1946), one case; Vorhaus and Rothendler (1946), two cases; Manganaro (1946), one case; Tyson *et al.* (1946), five cases, but in this series there was one patient who died forty-eight hours after admission without receiving penicillin, a second patient who was treated with penicillin but succumbed to an underlying cardiac condition, a third patient who succumbed in spite of what was thought to have been adequate dosage of penicillin, and a fourth patient who died ten hours after admission after only one day of treatment; Boland *et al.* (1946), one case; Thomas (1946), one case, Mackenzie (1947), one case, and Morton (1947), one case, but the latter observer also treated another case in which he did not seem to be able to control

the severe infection, for though the white count rose to 5000 the polymorphonuclears only reached 16 per cent and the patient died. Vorhaus and Rothendler (1946) made a plea for the use of 1,000,000 units of penicillin daily in agranulocytosis, believing that lower dosage than this is likely not to be adequate in some instances.

Streptomycin.—Seligman and Weintrob (1947) reported the successful employment of streptomycin in a patient who was not responding satisfactorily to penicillin

Pentnucleotide.—The hypothesis of leukocyte disintegration products as stimulants of leukocyte production is enticing but it is not certain that very much of practical value has accrued from it, however, it would require more

withhold use of the agent in

on, who introduced pentnu-

40 cc. be given intramuscu-

dosage, giving 10 cc. every

pentnucleotide in 540 cc. of normal saline was allowed to drip intramuscularly at the rate of 10 drops a minute and was continued for three days, 120 cc. of pentnucleotide being given in all; thereafter 10 cc. was given intramuscularly twice daily for three days and 5 cc. twice daily for a further six days. As a matter of fact, however, these authors felt that recovery in their case was spontaneous and not the result of their use of the pentnucleotide. This agent sometimes causes fairly severe systemic reactions.

Blood and Marrow Transfusion.—Since no technically satisfactory method of transfusing leukocytes alone is at present available, whole blood transfusions are resorted to, but it must be admitted that the rationale of the method is open to legitimate doubt since the transfusion of 500 cc. of blood can theoretically raise the leukocyte content of the recipient's body by only 6 per cent. However, it is the consensus—though not the unanimous opinion—that transfusion does no harm, and it would certainly be difficult to withhold the measure in a patient not responding well to penicillin. Fisher *et al.* (1947) gave multiple transfusions in three of their twelve cases. Ling and Tai (1946) recorded two cases apparently benefited by intrasternal transfusion of 3 to 5 cc. of marrow fluid from healthy donors.

Pyridoxine (Vitamin B_6).—Cantor and Scott (1944) gave pyridoxine hydrochloride intravenously in doses of 125 to 200 mg daily in three cases of

y unrelated

one blood

ransfusions

and pentnucleotide in large dosage were employed in addition to the pyridoxine In each of the three cases, however, the symptoms cleared up rapidly after the pyridoxine therapy was instituted and it was felt that probably this agent acted by direct stimulation of the myelocytic elements of the bone marrow. Piney (1946) said that the use of pyridoxine has completely changed the prognosis of agranulocytosis due to the use of thiouracil, rarely more than two 100 mg. doses being needed, he said he believed also that pyridoxine had improved the outlook in agranulocytosis due to other agents.

However, I have *not seen a record of the observations* substantiating Piney's statement.

BAL.—This agent has been very effectively used when an organic arsenical had precipitated the attack; see the treatment of arsenical reactions in *Syphilis for full discussion.*

THE PURPURAS

Nowhere in medicine today is there greater confusion than in this subject of the purpuras, the reason being of course our lack of knowledge. I am sure the present article will not satisfy specialists in this field; it certainly does not satisfy me, but it *represents* the best I *have been able to do within* the limitations of space and time and my own inadequate *grasp of the subject.*

Primary Purpura (Thrombocytopenic and Nonthrombocytopenic Purpura).—This entity, which is probably the one with which Werlhof was dealing in 1735, is preeminently a disease of the young, though no age is exempt; females are more often affected than males. In the classical form of the disease there is marked diminution in the number of circulating blood platelets, which may be brought out by repeated counts if a single one does not demonstrate it; prolonged bleeding time and little or no clot retractility; normal or nearly normal coagulation time; evidences of normal blood regeneration; and usually a positive capillary fragility test. Aggeler *et al.* (1946) determined from a study of sixty-four normal subjects and 404 patients suffering from various diseases that the normal range of platelets is between 273,000 and 545,000 per cubic millimeter, the critical level below which abnormal bleeding is likely to occur was observed to be approximately 100,000, though counts as low as 100,000 were obtained in one patient without abnormal bleeding and as high as 280,000 in another patient with classical primary thrombocytopenic purpura. Capillary *fragility* was found to be increased *in approximately* three-fourths of the patients with primary thrombocytopenic purpura, in one-half of those with secondary thrombocytopenic purpura, and in less than one-half of those with thrombocytopenia without bleeding or *with thrombocytopenia complicating* other *hemorrhagic states.* The spleen is usually not palpable in primary purpura. Spontaneous capillary hemorrhages may occur into any of the tissues, bleeding from the uterus, nose and mouth, and into the retina being the most common Hemorrhage into basal ganglia may cause fever, mental disturbances, convulsions, etc. The bleeding often begins without warning and persists intermittently for days or weeks, death resulting in severe cases from exsanguination. A chronic form of the disease is recognized, which does not develop from the acute form but is chronic throughout. These patients give a history of having bruised and bled easily for many years before the onset of the attack in which diagnosis is made from the blood findings. Such individuals bleed intermittently during a number of years, some dying and others apparently recovering completely. Cases have been reported in which a rapid fall in platelets and the appearance *of purpura were* associated with menstruation, with remissions between and recurrence with the succeeding periods; in- ... normal women

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cases in which menorrhagia was the only or the first symptom of thrombopenic purpura Congenital purpura seems to be an established fact: Davidson (1937) reported a purpuric infant born to a mother whose platelet count had always been low during the several years after the removal of her spleen because of purpura; Whitney and Barritt (1942) reported the case of a woman who, becoming twice pregnant after splenectomy for thrombocytopenic purpura, in each instance was delivered of an infant that succumbed to thrombocytopenic purpura in the neonatal period Patterson (1946) reported the case of a woman who had had chronic thrombocytopenic purpura since the age of four, who became pregnant against medical advice but went through pregnancy normally except for postpartum hemorrhage that was not too difficult to control, but whose baby was born with purpura. Barclay (1945), Schefrin and Shechtman (1945), and Waters (1946), each reported a single instance of a purpuric infant born of a non-purpuric mother. There seems to be also a very rare type of thrombopenic purpura (Altschule, 1942) characterized by the formation of numerous platelet thrombi in the capillaries throughout the body, rapid progression, failure to respond to transfusion and splenectomy, and the uniform occurrence of icterus and cerebral manifestations.

In primary purpura Dameshek and Miller (1946) found megakaryocytes considerably increased in numbers in the bone marrow but platelet production by them greatly diminished Some students of the disease contend that the spleen removes excessive numbers of platelets from the circulation, Troland and Lee (1938) reported that a substance extracted from the spleens of patients with thrombocytopenic purpura and injected into rabbits caused a reduction of circulating platelets in these animals—after several independent workers had failed to confirm the findings, Rose and Boyer (1941), Cronkite (1944), and Moolten (1945) seem to have confirmed and extended them. Madison (1946) seems to think, however, that abnormal permeability of the vascular walls for erythrocytes, concomitant with and possibly secondary to some alteration of the normal contractility of these walls, is responsible for most cases of primary purpura and that reduction of the thrombocytes and resultant impairment of the clotting mechanism only occasionally occurs. The animal experiments of Quick *et al* (1946) led them to surmise that perhaps the hyperpermeability of the capillaries and the thrombocytopenia are both caused by the same unknown agent.

Secondary Purpuras.—Purpuric manifestations are observed during the

anemia; acute leukemia; excessive irradiation; senility; cachectic states, especially if due to malignant disease, chronic liver and kidney disease. It is thought that these purpuras are not of the thrombopenic sort as a rule, save in instances when direct disturbance of bone marrow function has occurred, but as a matter of fact the group has not been exhaustively studied The purpuric signs disappear with recovery from the primary disease, de-

purpura the attack begins
pains, all of which usually

precede by some time the eruption which often partakes of the nature of purpura, urticaria and erythema in combination. Or there may be abdominal

to be ascribable to alterations in capillary permeability, which are believed to rest upon an allergic basis.

THERAPY

Unquestionably the most important single factor in treatment is to make

wise the failure to recognize an underlying drug intoxication, or an ascorbic acid or vitamin K deficiency or a neoplastic malady or leukemic blood dyscrasia, might have the direst results. The subject is confusing admittedly, but accurate diagnosis is mandatory notwithstanding.

Primary Purpura.—*The Allergic Approach*.—A sufficient number of case reports has now accumulated to warrant the careful study of every patient from the standpoint of drug sensitization; instances in which attacks have been definitely ascribable to the following agents have come to my attention: *organic arsenicals, gold salts, iodides, benzol, sedormid, nirvanol, phenobarbital*, quinine, ergot, dicumarol, sulfonamides; cases have also been reported in association with the use of hair dyes and leg stocking color preparations. Foods to which the patient responds allergically have also been indicted. Squier and Madison (1937), by limiting treatment to such dietary manipulation as eliminating foods suspected on the basis of history and skin tests, were able to effect striking clinical improvement and gradual marked rise in platelet level in their three patients. Dutton (1938) reported similar success in the single case which he treated in this manner, and Farrar and Roxby (1943) demonstrated the allergic nature of one of their cases. Madison (1946) has more recently said that in their continuing experience the allergic approach has been the most satisfactory one in thrombocytopenic

idical procedure,

that meticulous

ses it seems un-

fortunate that more of them are not submitted to such study. Schwartz

it was his feeling that marrow eosinophilia indicated an allergic state.

Splenectomy.—In 1947, Kracke, not himself a surgeon, reiterated his belief that splenectomy is the treatment of choice for primary, thrombocytopenic purpura. He had earlier said "I have never seen a severe case of this disease that finally did not require splenectomy. . . . It seems to me that treatment

abdominal incision has been closed.

experience at the Spleen Clinic of the Presbyterian Hospital in New York that an arrest of symptoms may be expected in approximately 85 per cent

of cases treated by splenectomy It is probable that the mortality associated with splenectomy in the hands of the general surgeon is in the neighborhood of 10 per cent, but certainly in specialized clinics the figure is much lower than this. Curtis and Movitz (1946) said it had been their impression in a series of more than 200 consecutive splenectomies that older patients recovered fully as well as younger ones These authors also emphasized the fact, earlier mentioned by other observers, that the end result of splenectomy is to a degree dependent upon whether or not accessory spleens have been found and removed, they reported four instances of recurrence of symptoms subsequent to splenectomy, in all of which accessory spleens were found and appeared to be the cause

Transfusion—The object of transfusion in purpura is not solely to supply blood lost through hemorrhage, since the anemia usually rapidly disappears through the body's own spontaneous efforts once bleeding ceases, but also to introduce platelets in the hope of stopping hemorrhage, Madison (1946) says that transfused blood may also exert a favorable influence upon vascular erythropermeability It is interesting to note that the native African disease "onyalai," now considered to be essentially thrombocytopenic purpura, has been shown by Stein and Miller (1943) to respond well to full transfusions of blood

Splenic Irradiation—Most men have not as yet become convinced of the worth of this measure However, Madison, Squier and Morton (1943), of Milwaukee, reported a small series of cases which suggested to them that irradiation might be a valuable temporary measure in stopping spontaneous vascular leakage in selected cases of purpura whether or not there is an associated thrombocytopenia or hypoprothrombinemia. They felt that if such an association exists it is important to eliminate the vascular leakage promptly, and further that failure of response to irradiation strongly suggests that purpura is secondary to progressive malignant disease, while on the other hand satisfactory response may suggest that if other therapy fails splenectomy is likely to be beneficial Madison (1946) said that favorable response to splenic irradiation does not rule out an allergic type of purpura and that there is considerable evidence to suggest that allergic purpuras are likely to be improved by splenic irradiation

Rutin—Growing out of the belief that avitaminosis C was of etiologic importance in thrombocytopenic purpura came the studies with citrin (vitamin P), a substance derived from paprika or lemon and capable of reversing experimentally produced vascular fragility Subsequently two crystalline derivatives of citrin, hesperidin and eriodictyol, were tried but it was never shown that they were really effective therapeutic agents. The latest addition to the agents of this type is rutin. which is closely related chemically to hesperidin and is principally obtained from buckwheat It seems that rutin is of very low toxicity, if indeed it has any appreciable toxicity at all for man; it is available in the form of small tasteless pellets to

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tion of the use of the drug resulting in relapse and resumption in remission

in these cases, but less convincing results were seen in the allergic, and questionable results *in the remaining groups.* Kushlan (1947) called attention to the fact that the sulfonamides seem to interfere with the action of rutin; he felt that if they must be employed *the dose of rutin should be doubled or* tripled.

Seconday Purpura.—The treatment is that of the underlying major disturbance, perhaps in some instances with transfusion, as indicated.

Schönlein-Henoch's Disease.—The fact is well established that these attacks are practically always of an allergic nature, treatment therefore consists principally in the search for the guilty allergen and the attempt to eliminate it from the diet or environment or to desensitize the patient to it. Of course splenectomy and all other drastic measures are contraindicated; cases are on record, however, in which laparotomy has revealed intussusception and true hemorrhagic appendix.

HEMOPHILIA

Hemophilia is an hereditary hemorrhagic disease of unknown etiology, transmitted by the female but occurring only in the male. Macklin's (1928) studies showed that (a) a man afflicted with hemophilia will have no hemophilic children provided he marries a woman who is not a carrier; (b) the sons of such a man will be normal and unable to transmit the defect; (c) his daughters will all be carriers, though outwardly normal, liable to give the active disease to half of their sons; (d) half the daughters of a woman who is a carrier are apt to be carriers themselves, transmitting the defect, as their mother did, to half their sons as the active disease, and to half their daughters who will be carriers *in their turn; half the daughters and half the sons* of a woman who is a carrier are apt to be normal, (e) since, in a hemophilic family it is impos-

[illegible]

males and their descendants. Macklin's [illegible] later study [illegible]

[illegible] disturbed in hemophilic

[illegible] *the*

[illegible] into

the classical framework, but these pages are of [illegible] any analysis of such rarities.

The *characteristic* abnormality in the blood of individuals with classical hemophilia is prolongation of the coagulation time, an alteration, however, which varies apparently from day to day and perhaps even from hour to hour;

[illegible] to bleed than at

[illegible], and the platelet

[illegible] the Rumpel-Leede [illegible] erythropermeability

[illegible]

[illegible] thromboplastin were sluggishly [illegible]

[illegible] plasma several

[illegible] transforma-

[illegible] content of

citrated hemophilic plasma. Quick (1947) has presented findings seeming to show that the platelets are essential for coagulation since they appear to be required for the activation of thromboplastin that he believes to be present in the plasma in an inactive form, it seems that Lenggenhager (1946) had earlier postulated the presence of this inactive precursor of thromboplastin in the plasma. Quick believes that the platelets on disintegration liberate an enzyme that acts specifically on the thromboplastin precursor. He feels that in hemophilia the platelets are normal but that they are unable to function in the conversion of the precursor since it is not present in an available form in the blood of victims of this disease It seems almost certain that neither calcium nor fibrinogen disturbances are present in hemophilia. In the years since 1936, independent groups in Boston and in Amsterdam have been presenting evidence in support of the view that blood plasma contains a specific antihemolytic globulin that accelerates clotting and is deficient in hemophilic blood The findings seem to indicate that the antihemolytic factor is neither prothrombin nor fibrinogen.

Hemophilia usually makes itself apparent at an early age External hemorrhage of an oozing type occurs following the most trivial injuries, spontaneous bleeding in the viscera is rare, except in the kidneys, and bleeding into the central nervous system is very unusual Obstinate epistaxis is common, so also are hemorrhages into the muscles and skin and about the joints; the latter ultimately cause deformities much resembling those of tuberculosis or low-grade arthritic conditions, but in the acute stage differentiation must be made from traumatic synovitis, acute rheumatic fever, acute pyogenic arthritis, gonorrheal arthritis and osteomyelitis Skold (1944), in Sweden, has estimated that in hemophiliacs the risk of death during the first year of life is not abnormal, but in the first decade it is 6 8 times, in the second decade 4 9 times, and in the third decade 7 5 times greater than in the normal

In the Babylonian Talmud (second century, A D) it is stated that circumcision is to be discontinued in a family in which it has caused two successive fatalities, this is looked upon as the earliest reference to hemophilia in any literature, according to Skold (1944), the first description of hemophilia made by a physician was that of Albukasim, who died in 1107 The first clear account in modern literature was that of Otto, in 1803, the disease was named by Schönlein in the middle of the nineteenth century Hemophilia is of exceedingly rare occurrence in Negroes

THERAPY

Blood transfusion usually hastens coagulation for a period which is long enough for clotting to take place, the duration of the effect of a transfusion is highly variable but is usually a matter only of hours and not of days, so that unless one of the nonbleeding phases characteristic of the disease happens to begin shortly after a transfusion is given it is apparent that transfusion is of very limited value as a measure to keep the patient alive indefinitely. It seems that 100 cc is as effective as 500 cc Patek (1940) felt that unless the patient urgently needs hemoglobin a transfusion of 100 cc at twelve-hour intervals is preferable to 600 cc at three-day intervals, he also found pooled citrated plasma just as effective as whole blood Johnson (1942) successfully used plasma which had been prepared for storage by the now familiar lyophile method, and others since have done the same Sköld (1944) had the unique opportunity of studying the survival of erythrocytes in the case of a patient

who had ovalocytosis and in whom it was observed that the round erythrocytes were still present in the blood stream thirty days after a transfusion; there is, however, no evidence indicating that the coagulation-promoting substances remain active for the same length of time. Munro (1946) described the recovery of an anticoagulant from the plasma of a hemophilic patient who apparently as the result of frequent transfusions had developed a phase in which further transfusions failed to cause either a reduction in his coagulation time or clinical improvement. In 1932, Lawson *et al* not only did not transfuse their patient, but since severe hemorrhage results in decreased clotting time, they actually deliberately bled him. Five hundred to 600 cc. were withdrawn every five to six weeks, apparently with good symptomatic results; indeed, in a subsequent report, it was stated that this patient had been bled about once every six weeks with good results until the time of his death in another hospital in 1939, the successful employment of venesection in hemophilic crises in two other members of this patient's family was also reported. However, Sköld (1944) said that at the express request of a patient he performed venesection on one occasion but saw no influence on the coagulation time. Hemophiliacs appear to have an accelerated rate of blood production, which insures rapid recovery from hemorrhage of ordinary extent; iron therapy is sometimes helpful, but liver-stomach preparations are not needed These individuals, especially those who are only mildly afflicted, can be carried safely through surgical procedures if transfused just before incision and repeatedly during the healing stage of the wound—but it is the part of

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been

under study in their Boston group for a number of years was comparable in its antihemophilic effects with that obtained by the injection of whole blood or plasma. But since this Fraction I contains the fibrinogen of blood plasma as well as small amounts of prothrombin, and the earlier work of this Boston group had indicated that neither of these proteins was responsible for the antihemophilic properties of plasma, these two proteins were prac-

if we get such a product it will only serve to do through the injection more concentrated agent what is done by the transfusion of blood or plasma, namely to effect coagulation of the hemophiliac's blood for a few hours. The defect in hemophilia is an hereditary one and not likely easily to be overcome by some "factor" that we learn to inject; in fact, if we tamper too much with the clotting mechanism of the hemophiliac he may learn to combat these procedures with the development of unpredictable processes designed to maintain what for him is possibly a physiologic state of poor blood coagulability, and this thing that we force upon him may be harmful to him.

Sutton (1946) reported the successful checking of bleeding from an amputation stump by the local application of plasma, but since the patient was also being given transfusions at the time it was difficult to know to what extent the local application was really effective. This same observer reported that 2 ounces (60 cc.) of plasma given in milk by mouth three times daily was an effective prophylactic and therapeutic measure in hemophilia and that plasma applied to a pad with the patient biting on it is effective in

nose and mucous membranes of the mouth can to a great extent be checked by cautery and that in tooth extractions he transfuses with 400 cc. of blood and then, simultaneously with the administration of the local anesthetic, injects freshly prepared plasma into the gums, the blood being centrifuged but a few minutes in preparation of the plasma so that the thrombocytes still remain. Sometimes Skold has found it necessary to transfuse after the operation and in some instances to apply a tampon thereafter. The antihemophilic globulin substance of the Boston group is said to act as a local hemostatic when applied to the bleeding point in dry powder form with adequate dressings. Another globulin preparation with strong coagulating action when applied locally is that obtained from human, bovine, rabbit or swine plasma by a "salting out" process; Lewis *et al* (1946), of the Boston group, said that from a practical point of view this hemostatic globulin is definitely superior to the antihemophilic globulin in the local control of hemorrhage since its action is immediate. Apparently the rabbit hemostatic globulin does not cause untoward local or systemic reactions.

HEMORRHAGIC DISEASE OF THE NEWBORN

(See *Vitamin K Deficiency*)

HYPOPROTHROMBINEMIA

(See *Vitamin K Deficiency*)

HEMORRHAGE IN OBSTRUCTIVE JAUNDICE

(See *Vitamin K Deficiency*)

CIRCULATORY DISEASES

FUNCTIONAL DISTURBANCES OF THE HEART

Occasionally a functional heart disturbance in an individual of fairly robust mental and physical status will follow upon the shock of a sudden cardiac death in a near associate, but cardiac neuroses are usually seen in persons of definitely neurotic type and often with a history suggestive of neurotic ancestry. There is complaint of transitory palpitation, rushing of blood in various parts of the body, throbbing and many other symptoms described with the particularity habitual to the neurotic. When there is pain it is usually felt over the left chest where the heart is supposed to be rather than under the sternum. In the condition known as neurocirculatory asthenia (effort syndrome, soldier's heart, irritable heart), the symptoms—giddiness, faintness, palpitation, precordial pain and breathlessness—are the symptoms of effort and mark the patient as one who is physically inadequate to the ordinary stresses and strains of an active life. In War I effort syndrome was a serious problem especially in the British Army, but Jones and Scarisbrick (1942) stated early in War II that the number of cases being encountered was proportionately much smaller, in our own country, too, every effort was made to screen out these individuals at the induction centers, but in spite of this effort Brown (1944) was obliged to report that in a twelve-month period at a large Army hospital there were nearly ten times as many soldiers with this syndrome as with organic heart disease However, Hill and Dewar (1945), writing toward the close of the War, said it was generally agreed, though exact figures were still lacking, that the incidence was less in War II than in War I; at a hospital in the Middle East in which all cases of effort syndrome in the Force were centralized they constituted less than 1 per cent of the 25,000 medical and surgical cases admitted to the hospital in twenty months. As a result of studies upon Navy personnel, Master (1944) stated his belief that effort syndrome is really the result of a congenital or constitutionally small heart and should therefore no longer be considered merely a nervous or functional disorder. Friedman (1945), however, concluded from his study of fifty cases that the heart is normal in size, structure and function at rest and also during effort if unaccompanied by emotional activity, but that changes in the rate, rhythm and force of cardiac contractions are preceded by or associated with excitation of the sympathetic nervous system resulting from hypothalamic discharge In 65 per cent of Steven's (1945) forty patients there was a flat sugar tolerance curve

THERAPY

Patients with undoubted cardiac neuroses comprise a very considerable portion of the "heart" cases seen in an average general practice, and the fact that the elements of their treatment can be set down in a relatively few lines of print by no means justifies a contemptuous attitude toward the group. The more robust will be cured by complete examination and the reassuring statements of a doctor in whom they have confidence, but what is needed

by the majority of the patients is just exactly the hardest thing in the world [illegible]

[illegible]

with his circulatory apparatus, but there are ways and ways of assuring him of this fact Perhaps the best method is to demonstrate his freedom from symptoms while enjoying some diversion in which he is for a time free from his inordinate load of cares, to ridicule or to scold is almost certain to toss him to the quacks

[illegible]

as well, is desirable White (1942) said that it was found [illegible]

[illegible]

when they were excused from certain duties they [illegible]
Brown (1944), started an epidemic of the same symptoms [illegible]

PERICARDITIS

Acute pericarditis rarely occurs except as a complication of [illegible] tious diseases, particularly tonsillitis, sinusitis, tuberculosis, [illegible] acute rheumatic fever, pneumonia and sepsis (septicemia, [illegible]

[illegible]

graphic or physical findings are of positive aid. The *prognosis in fibrinou* pericarditis is always good; in the effusion cases, if the fluid is *tuberculous o* becomes purulent (suppurative pericarditis), death is the usual outcome, bu in rheumatic cases the fluid is usually *resorbed. Acute pericarditis was prob ably first discovered by Avenzoar, of Cordova, in the twelfth century.*

There is also a chronic type of constrictive pericarditis known as "Pick' disease." Its chief characteristics seem to be (a) insidious onset *of dropsy i* a young person without nephritis or a markedly abnormal heart; (b) enlarge *liver, ascites and prominence of jugular veins; (c) low systolic arterial pressur* and a small pulse pressure and paradoxical pulse. History of antecedent pericarditis or polyserositis is a helpful clue. The patients are condemned to semi-invalidism unless properly treated.

THERAPY

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of opiate-like action on the gastro-intestinal tract. Salines, or enemas, are definitely indicated to prevent abdominal distention or straining at stool, both of which increase the load upon the heart. Aspiration of fluid brings such great relief in the effusion cases that it is held to be advisable to *employ* the procedure early and f

remarkably quick sub

and Loughlin (1945),

others have reported

aspiration of the exu

units in 10 cc of normal saline following the aspiration of 15 cc. of fluid.

In Pick's disease the outlook has been completely changed through the introduction of surgical technics facilitating removal of a portion of the thickened pericardium; relief of symptoms and "cure" often result. In preparing these patients for operation, Stewart (1942) said that he restricts the salt and fluid intakes, uses a high protein diet and diuretics, and does not give digitalis unless there is a superimposed auricular fibrillation.

ENDOCARDITIS

develops dur-

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ver.

Precordial pain, increase in pulse rate, murmur and often a consid dila-

tation of the heart appear later *Acute bacterial* endocarditis is also usually a

are sometimes prominent also Some of these cases

have earned the appellation "malignant endocarditis." Then there are the cases of *subacute bacterial* endocarditis in which the patient with a preexisting

valvular lesion experiences a reinfection of the endocardium from an infectious process in the teeth, tonsils, middle ear, or other focus. Rheumatic valvulitis and congenital cardiac lesions are the most common precursors of this form of endocarditis, a nonhemolytic streptococcus the organism most often in the etiologic role. The disease runs an obscure febrile course until a murmur of

nodules occurring either intracutaneously or subcutaneously as the result of minute bacterial emboli in the superficial terminal vessels in the pads of the fingers or toes—is pathognomonic of this affection. Christian (1941) said that if malaise and fever, joint or muscle pains, nausea or loss of appetite appear in an individual, usually a youth or young adult known or found to have chronic valvular or congenital disease of the heart, and persist for more than one week without the development of evidence of other definite disease, the probability

(1945), in reporting two cases of their own, brought the total number of

I believe that Matthew Baillie (1761–1823) was the first to describe endocarditis.

THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

In all forms of endocarditis the patient must be kept absolutely quiet, to which end the use of the ice-bag, or in the asthenic individual hot applications, over the precordium is indicated; opiates should be used if pain and restlessness are severe. For a discussion of the effect of salicylates in the rheumatic type of the disease see Rheumatic Fever. Acute bacterial (malignant) endocarditis is best treated as a case of sepsis, the symptoms of which, indeed, usually dominate the picture; fever therapy seems to be of adjuvant importance in the gonococcal cases.

Penicillin.—There seems to be no doubt now that the efficacy of penicillin therapy in the treatment of subacute bacterial endocarditis is fully established. Seabury (1947) reported that of the twelve patients treated by penicillin at the University of Michigan Hospital seven apparently experienced a successful

cases but the percentage of cures remains about the same. That this chemotherapeutic victory is a somewhat Pyrrhic one, since many of the patients are enabled to survive the disease through the agency of penicillin only to die later of congestive heart failure, is not the fault of the drug, for Fiese (1947), who considerably studied this matter, found that cardiac failure is important or potentially so in a large majority of untreated patients with subacute bacterial endocarditis, 80 per cent of his series of forty untreated patients followed to autopsy having shown evidence of cardiac failure of

more or less chronicity. He found that statistically treatment with penicillin actually postpones cardiac failure and reduces its incidence. As for dosage, the experience of Hildebrand and Priest (1947) led them to adopt 500,000 units daily as the minimal amount to be employed, for they followed patients to autopsy and found that the degree of healing was definitely related to the adequacy and the duration of the treatment. This figure seems about to express the feeling of most men of experience. Priest *et al.* (1947) concluded that the highest percentage of cures is to be obtained when the drug is given by continuous intravenous drip, the day's dose of penicillin being dissolved in a liter of physiologic saline solution and the rate of flow adjusted so that this amount is delivered in twenty-four hours with the needle of course anchored in the vein. They recognized the possibility of pulmonary embolism resulting from continuous venoclysis but believed it to be a remote one; they also admitted venous irritation and thrombosis but said that this occurs much less frequently with the newer preparations of penicillin. However, they made the point that 5 per cent dextrose or distilled water should not be used since to do so is to invite thrombosis. Continuous intrasternal and subcutaneous infusions have been tried by this group in single instances without satisfaction. With regard to dosage it should be noted that the minimal 500,000 units per day previously referred to as being established by Priest's group refers only to their continuous intravenous infusion method, their material not permitting of any definite conclusions regarding minimal optimum daily dosage by intramuscular injection In discussing the serum level of penicillin that should be attained, Priest *et al.* said that they had not observed a single cure in which the mean serum level was not considerably above 0 5 units per cc , though only eight of twenty-six organisms titrated required more than 0.1 unit of penicillin per cc. for *in vitro* inhibition. The reason for this discrepancy is probably the assumed lowering of concentration of penicillin during its deep penetration into the fibrin of the vegetative processes, a fact that seems to have been established by Nathanson and Liebhold (1946). Regarding duration of treatment, Priest *et al.* (1947) established four weeks as the minimum, since with one exception anything less ... failure in their experience regardless

many weeks it takes. In this matter of dosage it is well to note, however, that *one cannot safely fix a minimal dosage* without taking into account the organism with which one is dealing, for there are some organisms *that are* notably resistant to penicillin. For example, Loewe *et al.* (1946) reported ... *only recently recognized* as associated with subacute ... in combating it the ... *et al.* (1947) have therefore taken the position that *if after four to six weeks'* administration of 500,000 units per day by continuous intravenous drip the patient is not doing well clinically the dose is to be increased to 2,000,000 units per day ... *experience may* show that such a radical ... do anything else at present. ... before beginning treatment to be one unit or more per cc., *they start with* 1,000,000 units per day and do not hesitate to increase to 2,000,000 units and even more if the clinical course is unfavorable. Jones and Tichy (1947) feel that the best method is

blood level five to ten times higher he organism *in vitro*. They say that r be necessary to give as much as 5,000,000 units daily, as was the case in the patient under treatment at the time they wrote, but that cannot be helped. They feel there is no significant difference in the percentage of cures when either intermittent intramuscular injection or continuous intravenous injection is employed provided sufficient penicillin is used in either method.

The Effect of Anticoagulants on Penicillin Therapy.—Priest *et al.* (1946), studying the use of heparin as well as dicumarol, found that these agents exerted no influence on the dosage of penicillin, had no influence on the formation of fibrin, did not affect the length of time over which therapy was required, and doubtfully prevented major embolism They did find, however, that in general thrombosis at the site of the needle when the penicillin was being given by intravenous drip was less in patients receiving heparin incorporated in the penicillin-saline mixture (50 mg. of heparin added to the mixture). Dawson and Hunter (1946) found that results with penicillin alone were slightly better than with heparin added and it was their impression that fewer embolic phenomena occurred when heparin was omitted, while of course the risk of hemorrhage was avoided and the treatment greatly simplified. However, they recognized two possible indications for the use of heparin. first, they felt that in some instances in which large emboli have lodged in major vessels it might be advisable to heparinize the patient in order to prevent retrograde thrombosis in the artery and thus to keep the collateral circulation open, and second, when extremely large doses of penicillin of such order as 5,000,000 to 10,000,000 units per twenty-four hours are employed, thrombophlebitis at the site of intravenous infusion commonly occurs and they felt that heparin may be useful in minimizing this complication of therapy. However, they successfully administered 10,000,000 units per day by constant intravenous drip for as long as sixteen consecutive days without employing anticoagulant therapy One of the patients of Levy and McKrill (1946) died from a heparin reaction although she was free of all evidence of endocarditis at postmortem examination. Thill and Meyer (1947) expressed themselves as decidedly skeptical that any benefits are to be derived from the combined use of dicumarol and penicillin, and felt indeed that this procedure carries with it grave hazards in subacute bacterial endocarditis. They employed dicumarol in an initial dose of 4 or 5 mg. per kg, subsequent daily doses being 1.5 mg per kg to maintain a prothrombin time between 25 and 50 per cent of normal. In the first trials the use of dicumarol was begun shortly after initiation of penicillin therapy, but after the death of a patient following a few days of this combined therapy, possibly from cerebral hemorrhage, they initiated the anticoagulant therapy only after the temperature reached normal or below or after the cultures became negative.

Streptomycin.—Hunter (1947) recorded six cases in which streptomycin was used in therapy because the organism was either a streptomycin-sensitive gram-negative bacillus or a nonhemolytic streptococcus that was penicillin-resistant Of the three cases due to gram-negative organisms, streptomycin appears to have effected cure in two and failed in one, of the three patients infected with penicillin-resistant streptococci, only one responded to streptomycin and this patient *received large doses of penicillin in conjunction*. Combining his results with those obtained in twelve additional cases in other

clinics, Hunter said that probable cure has resulted in eight of the eighteen cases, though the role of streptomycin he felt was open to some question in four of these eight. He felt that when streptomycin is resorted to it must be

and a few nerve deafness as a result of this therapy.

Sulfonamides and Sodium Para-Aminohippurate and Urea.—Though the sulfonamides have in the main been a failure in the treatment of subacute bacterial endocarditis, there occur instances in which penicillin therapy alone fails to suffice and its combination with a sulfonamide is successful—witness the case of Priest *et al.* (1947), in which an organism of the parainfluenza group did not yield to eight weeks of penicillin alone in dosage up to 1,000,000 units

alone, but was overcome by a combination

which streptomycin would be

heparin, failed to sterilize the blood stream

was retarded during the year of this treatment When the patient was given 10 000,000 units of penicillin and 240 gm. of sodium para-aminohippurate

given alone in the orthodox manner, Vesell *et al.* (1946) resorted to the use of the agent in heroic dosage in combination with urea; 20 gm. of sodium sulfadiazine with 30 gm of urea in 1500 cc. of distilled water was given intravenously at such rate that the infusion was completed within two and a half hours. The patient was given two such infusions at an interval of twenty-four hours, on the four succeeding days was given intravenous infusions of saline and glucose because of the dehydration consequent upon nausea and vomiting resulting from the therapy, and then after a few days a second series of two sulfadia-

infusions was given and in a few days a third series. The patient was

d remained well for two years at

is treatment a blood concentration of 62 mg per cent free and 98 mg. per cent total sulfadiazine was recorded.

ACUTE MYOCARDITIS

Except for the relatively rare "acute isolated myocarditis," an entity

during or after an attack of

delayed or

THERAPY

The reader is referred to the article on Rheumatic Fever, particularly to the section on Bed Rest, etc.

CHRONIC MYOCARDITIS

(See *Chronic Nonvalvular Heart Disease*)

ARRHYTHMIAS NOT OF PRIMARY THERAPEUTIC INTEREST

There are properly three groups of cardiac irregularities first, those which might be called "normal" without too great impropriety, second, those which are entirely secondary to some other underlying pathologic process; and third, those which must be combated upon the basis of their own independent existence Obviously, in a book such as this, mere listing of the entities in the first two groups must suffice so that detailed attention may be given to the last, or therapeutically important, group In *sinus arrhythmia*, the heart rate gradually accelerates and retards usually synchronously with the phases of respiration; this occurs in all infants, many children and some adults, and disappears temporarily whenever the heart rate is increased in normal tachycardia; it appears occasionally during digitalis therapy and frequently as recovery from normal tachycardia takes place *Sinus* or *normal tachycardia* is the acceleration in regular rate that occurs in hyperthyroidism, fever, exercise, shock, anemia, etc.; the treatment is that of the underlying condition, Barker *et al.* (1943) used quinidine in five cases and found that the rate was either not affected or slightly increased, and in one patient a transient right bundle branch block occurred two hours after administration of the drug upon two separate occasions; in a well-controlled small series of cases having no apparent etiological basis, Waldman and Moskowitz (1944) aborted the attack by the intramus-

is called auricular standstill); first degree block, an increase in conduction time between auricles and ventricles, usually detectable only with the electrocardiograph; second degree or partial block, in which, due to failure of some of the impulses to reach the ventricles, the auricles and ventricles beat in a rhythm of 2 to 1, 3 to 1, and so on, and bundle branch block, an electrorcardiographically demonstrable delay or block of an impulse in one of the branches of the bundle of His *Ventricular fibrillation*, for which there is no effective treatment, is practically always only a terminal event. *Pulsus alternans* is not a true arrhythmia but an alternation in force of the regular beats; the treatment is that of the underlying heart disease.

PAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER

Auricular fibrillation is probably due to a self-perpetuating ring of excitation—"circus movement"—about the mouth of the superior vena cava, the auricles being maintained in rapid fibrillary contractions, to only a small number of which the ventricles respond. The pulse is extremely irregular in rate and unequal in force, and the count at the wrist, though usually high, is often less than at the apex due to the failure of some of the weak ventricular contractions to open the valves or initiate the wave; in rare instances the "pulse deficit" may be so great as to produce a rate at the wrist lower than normal. In auricular flutter the circus movement is slower than in fibrillation and it is responded to by the ventricles at a regular rate and in a definite ratio; *i.e.*, the relationship of ventricular-auricular impulses will be 1 to 2 or 3 or 4. Flutter is detectable only through study of the electrocardiogram.

Both of these arrhythmias, but especially fibrillation, have long been known frequently to complicate congestive heart failure from the usual causes, and likewise to appear not infrequently in advanced thyrotoxicosis. In recent years it has also been recognized that they may occur in a heart otherwise apparently entirely normal In these instances palpitation is the most common symptom, pain the rarest; sometimes there is breathlessness, pallor, vertigo and nausea. Usually the paroxysms do not last longer than a week, but rarely an attack has persisted as long as a year and then terminated spontaneously. During the attack of fibrillation exercise increases both the rate and irregularity of the contractions In Brill's (1937) case severe congestive failure appeared but entirely cleared up upon cessation of the arrhythmia Most of the patients are at or past middle age when their first attack is experienced, frequency of paroxysms is variable but tends to diminish with the passage of time; the studies of Orgain *et al.* (1936), and Willius and Dry (1941), indicated that the *prognosis* for life and for the maintenance of cardiac function is usually excellent.

THERAPY

The treatment of these arrhythmias when they complicate congestive failure from other causes is usually quite secondary to treatment of the failure itself; *i.e.*, when all that is possible has been accomplished by the use of digitalis, the advisability of using quinidine must be separately weighed

in each case—the matter is discussed in detail under Congestive Heart Failure. At present we are concerned only with fibrillation or flutter in otherwise normal hearts; *i.e*, in postoperative cases of thyrotoxicosis in which spontaneous return to normal rhythm has not occurred, and in individuals who experience such paroxysms as above described. In a fibrillation of this sort digitalis is not regularly of value and quinidine is the drug of choice. It was a patient with paroxysmal fibrillation who first brought to Wenckebach's attention, in 1912, the use of quinine in the malady; Frey's investigations later caused the substitution of quinidine sulfate for the older drug. Quinidine is very effective, and increasing experience has shown that serious reactions are of infrequent occurrence in patients whose hearts are normal except for the arrhythmia. However, there is not always need to use the drug in these cases, since most of the paroxysmal attacks suddenly terminate spontaneously in a few days.

Gold (1945) said that very rarely when one gives quinidine by mouth the first effect may be that the ventricular rate will go up considerably because quinidine blocks the vagus and accelerates the rate in much the same way as atropine Gold usually gives 5 grains (0 3 gm) every two hours until the fibrillation ceases, or throughout the day, if the fibrillation does not come to an end that day, the dose is doubled the next day and pursued in the same manner. He says it is rare that such doses fail and that they are without danger because the plan is interrupted when fibrillation ceases or minor toxic effects appear, such as buzzing in the ears or clouding of vision. Pardee (1945), in comment, added diarrhea as a toxic effect of the drug. Gold said that the system of dosage he uses for the case of paroxysmal fibrillation in order to prevent recurrences is to give one dose of 5 grains (0 3 gm.) three

size of the single doses. He says that it may take some time to attain the appropriate level of dosage but that the method is safe and sure; he has given as many as nine doses of 10 grains (0 6 gm) each in this way in twenty-

just be of interest in passing to note that Gertler and Yohalem (1947) have found that quinacrine (atabrine), when given intramuscularly in a dosage of 6 grains (0.4 gm.), may restore normal rhythm in cases of auricular fibrillation.

In auricular flutter it is the consensus that full digitalization should be preferred to the use of quinidine; the flutter is often converted into fibrillation which in turn ceases when digitalis administration is stopped. If digitalis *fails then quinidine is to be tried.*

PAROXYSMAL AURICULAR TACHYCARDIA

In this disturbance the patient becomes aware of a sudden great increase in the heart rate, usually to from 120 to 180 beats per minute. The rhythm is regular and the rate is not decreased during rest. Such a paroxysm may persist for hours or even for many days, and the attacks may recur frequently *during weeks, months, or years. Individuals* without demonstrable cardiac pathology are just as liable to these paroxysms as are the victims of heart disease; the young are more often affected than the old. Hubbard (1941) reported nine cases in infants under one year, and Weyler and Dustin (1942) the interesting case of a patient who presented this arrhythmia throughout the latter part of four pregnancies over a five-year period. Miller and Perelman (1945) reported two unusual cases in which the rate of the tachycardia varied markedly on change of position The attacks terminate just as suddenly as they begin, and in most instances without having caused any disturbance other than distress and palpitation; in rare instances, however, there are associated neurogenic symptoms such as polyuria, sweating and dilatation of the vessels of the skin. Mild symptoms of transient congestion have been occasionally recorded, but Grant's (1947) case seemed amply to confirm the old aphorism that this type of arrhythmia leads early to heart failure only in the previously diseased heart. *Wolff (1945) said that in the majority of* cases in which paroxysmal tachycardia induces anginal pain, coronary heart disease usually with angina pectoris is present; he believed that causes other than tachycardia must be suspected when collapse is associated with rates well under 200 or when termination of the abnormal rhythm or significant *reduction of heart rate is not promptly followed* by resumption of a normal circulation. Some men are beginning to be interested in the possibility of an allergic origin of paroxysmal auricular tachycardia.

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[illegible]

carotid artery below the angle of the jaw and sustained for ten to fifty seconds; pressure should not be made upon both sides at once Firm pressure over the eyeball is also often effective but it is painful There are individuals who can stop an attack by indirect stimulation of the inhibitory mechanism, such as by deep breathing or holding the breath, vomiting, swallowing a hard bolus of food, or by assuming various postures.

Acetyl-β-Methylcholine (Mecholyl).—Starr (1936) introduced the use of this drug, which causes effects analogous to vagal stimulation. The attack was

quickly terminated in 88 per cent of seventy-five instances in thirty-seven patients. In 20 per cent of the instances carotid pressure was effective during the period of the drug's action though it had failed before. Mecholyl is given subcutaneously in dosage varying, according to age and weight of the patient, from 1/6 to 1 grain (10–60 mg). The injection is followed by a sudden sensation of warmth in the face, hyperpnea, sweating and salivation, and sometimes a sense of tightness across the chest. Morgan (1943) gave a preliminary injection of morphine to lessen the perception of these disturbing symptoms. The patient should be supine when injected. In some instances of failure, repetition of the same or a larger dose after half an hour may bring success, Gold (1940) gave as much as 1 grain (60 mg) at one time intramuscularly, but the drug should never be given intravenously. Walsh and Sprague (1940) used 1/12 grain (5 mg) doses in a child of five years. One can add to the effect by vigorously massaging the site of injection. Nausea and vomiting are perhaps the
first symptoms of overdosage. An asthmatic attack seems to be precipitated in
susceptible individuals and momentary heart block has also been noted in a
few instances, coronary disease absolutely contraindicates the use of mecholyl.
Starr found that atropine sulfate, 1/50 grain (1.2 mg) intravenously, termi
nates any of these reactions almost at once. Morgan (1943) said he has a bloo
pressure cuff in place ready to prevent further absorption if necessary. It
felt that mecholyl is less effective when patients have been receiving quinidi
or digitalis, and that in any case it is drastic therapy not to be employ
unless other measures have failed.

Quinidine.—This drug is much used in combating the paroxysms; dos
reactions, etc., are considered under Auricular Fibrillation, failures occur
haps as often as successes. In the attempt to prevent recurrences, Gold (
preferred digitalis (see below) to quinidine.

Emetics.—Weiss and Sprague (1937) used the syrup of ipecac in fo
cases, successfully in each instance, this is an indirect method of stim
the vagus. Ideally, a dose of 1 to 2 drachms (4–16 cc) was given initia
repeated in the same or a larger dose if neither vomiting nor the desir
was produced in forty-five minutes, practically, however, it seems to h
necessary to develop the dosage, number of doses and time intervals s
for each patient. Gold (1940) seemed to have a high opinion of ipeca
also that not infrequently 1/20 grain (3 mg) of apomorphine hyd
will accomplish the same thing.

Digitalis.—Failure usually results from the use of this drug to
oxysm. However, a number of years ago Levine and Blotner pre
cases in which keeping the patient digitalized (beginning with fu
finally employing maintenance doses of approximately 2 grai
0.13 gm., per day) was effective in preventing recurrence in ind
to have many attacks during a year. This is a small number of
suggestive that the failure of most workers to get satisfactory
due to their small dosage of the drug, in his book Levine (1
this position. Gold (1940) also felt that digitalization, wit
double Levine's dosage, is the most effective safeguard aga
Tandowsky (1945) used cedilanid (lanatoside C) intraveno
attack in eight cases and then continued the administration
ing the frequency of attacks from 4.2 in a twelve-month p
fifteen-month period, the amount of the drug given intrave
attack was 1/40 grain (1.6 mg.) and the daily oral dose e

(0.5 mg.) in only one of the cases. Hubbard (1941) used digitalis with satisfaction in most of his infants under *one year. I think it interesting that* Peterman's (1946) patient, a six-year old child, did not respond satisfactorily to either digitalis, cedilanid or mecholyl but was completely controlled by the administration of digitaline Nativelle, 1½ grains (0.1 gm.) twice daily.

Other Measures.—*Boyd and Scherf (1943) injected 15 to 20* cc. of a *20* per cent solution of magnesium sulfate intravenously in about thirty seconds with success in all of their eight cases, but they said they would hesitate to employ the drug when marked myocardial damage was obvious or if there were *marked* intraventricular conduction disturbances or *gallop* rhythm present.

Boyd (1942) reported the termination of attacks through the intravenous administration of 1 cc of the commercial ampule preparation of metrazol.

Youmans *et al.* (1947), reasoning that moderate sudden brief rise in blood pressure might reflexly stop a paroxysmal auricular tachycardia since the cardio-inhibitory reflexes elicited by such a rise are strikingly sensitive in experimental animals, gave neosynephrine intravenously to each of four patients who had a normal blood pressure between attacks and a somewhat lower pressure during attacks. The injection was given during thirty seconds, allowing ample time for the blood pressure to return to the pre-injection level after each trial dose; the increasing increments employed were 0.15, 0 30, 0.50 and 0 80 mg. Accompanying a blood pressure rise of 30 to 50 mm. *Hg* there occurred a reversion of rhythm to normal in all of the patients in 45 to 60 seconds. Two of the four patients complained of mild precordial discomfort for a few minutes following the injection but this was the only unpleasant [illegible] skin [illegible] the [illegible] nt is [illegible] the realm of clinical experimentation for awhile before undertaking its routine employment to stop attacks of auricular tachycardia in view of the potential risk implied in the sudden raising of blood pressure

A good many years ago injection or removal of the stellate ganglion was suggested in patients stubbornly refractory to other methods of *treatment;* Schwab and Willis (1942) found records of the employment of this treatment in eleven cases with some improvement apparently being effected in all.

EXTRASYSTOLE

[illegible] the [illegible] and then there is a long pause before the next beat occurs, this com[illegible] pause, due to the occurrence of *an extrasystole* during the period of diastole, may be felt at the wrist and is usually equal in length to the time of two [illegible] when they occur over a long [illegible] oses [illegible] air- [illegible] any

demonstrable cardiac pathology, as is usually the case, extrasystole is quite without direct significance, but since this phenomenon sometimes heralds the beginning of serious heart maladies it is always incumbent upon the practitioner to make a thorough examination of his patient before pronouncing the matter of no moment. Some men are thinking of the possibility of an allergic origin in some instances of extrasystole.

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[illegible]

here, as in the arrhythmia to which reference has just been made, strychnine seems in some cases to have adjuvant value.

Papaverine.—Elels and Katz (1942) reported a small series of cases in which 3 grains (0.2 gm.) of this drug, taken orally four or five times daily, was highly effective.

Aminophylline.—It has been reported that coronary dilators will occasionally abolish this arrhythmia even in the absence of any cardiac abnormality. These drugs have the advantage of at least being free from danger when taken by mouth; see Index for methods.

HEART BLOCK

(Adams-Stokes Syndrome)

[illegible]
m
cu
noted, however, [illegible]
lesions of th
to be the se
diverticulum
ventricular dissociation when stimulated by esophageal dilatation probably secondary to cardiospasm, the reflex being mediated through the vagus in both its afferent and efferent paths The victims of this disease usually have [illegible]

This disease was described by Robert Adams, in 1826, and shortly thereafter by William Stokes—both leading members of the great Dublin school

of the first half of the nineteenth century—but Flaxman's (1937) interesting historical study revealed that descriptions had in fact been published before this time.

THERAPY

Atropine.—Atropine paralyzes the vagus endings and should therefore release the heart from vagal inhibition, but as a matter of fact we do not as yet definitely know to what extent the ventricles are under this control. It is known, however, that vagus tone as a whole in man is greatest under thirty years and markedly decreases after fifty—which fact in itself would be quite sufficient to explain the usual failure to quicken the heart in Adams-Stokes disease, most of whose victims are elderly. However, in the case of Correll and Lindert (1947), previously referred to, novatropine in 1/12 grain (5 mg.) dosage was successfully used despite the fact that the patient was in the seventh decade

Other Drugs.—*Epinephrine.*—Epinephrine is used because of its well-known ability to stimulate the sympathetic innervation of the heart and thus to cause an increase in rate. Dosage is 0.3 to 0.6 cc. of the usual 1/1000 solution, subcutaneously, never intravenously. In dire emergency the drug may be injected intracardially, going into the fourth intercostal space at the upper border of the fifth rib close to the sternum. *Ephedrine.*—There have been several reports of success with this drug in a single or small series of cases but doubtless it has failed in many more unrecorded instances. The starting dose should be only 1/8 grain (8 mg.); full dosage is 3/8 to 1/2 grain (24 to 30 mg.), three or four times daily by mouth. *Barium Chloride.*—This drug was introduced a number of years ago in the attempt to increase the irritability of the ventricles. Initial dosage is usually 1/2 grain (30 mg.) three or four times daily by mouth; Gold (1940) said that sometimes one

normal individuals, has been disappointing. *Vasodilators.*—Such drugs as aminophylline and the nitrites, as used in angina pectoris, are tried, as what drug isn't? *Metrazol.*—Myres (1941) obtained symptomatic relief with this drug in his two cases, using one $1\frac{1}{2}$ grain (0.1 gm.) tablet three times daily. *Paredrine.*—Th

dosage in their

at intervals of

was helpful.

PAROXYSMAL VENTRICULAR TACHYCARDIA

This arrhythmia is usually associated either with acute myocardial infarction or with digitalis intoxication. Its therapy is considered in the article on Coronary Insufficiency and Occlusion.

CHRONIC NONVALVULAR HEART DISEASE

(*The Failing Heart of Middle Life, Myocardosis*)

A very large proportion of the patients in whom symptoms of cardiac derangement have developed after the age of forty may be classified under this present head They have neither endocardial, pericardial, valvular nor coronary lesions, and their disability seems to depend entirely upon inefficiency of the muscle. The cases may be placed more or less satisfactorily in Christian's three groups: (a) Patients who at any age complain of great exhaustion or of palpitation following slight exertion. They do not have true dyspnea but experience uncomfortable sensations in connection with respiration, perhaps have some substernal distress, and are sensitive to pressure in the region of the apex, and their heart rate is easily accelerated. Examination reveals a normal heart, but with perhaps a few extrasystoles and a rather tapping pulse, there are no evidences of past or present edema or passive congestion Usually an adequate cause for the condition can be found in antecedent infections, in debilitating diseases with a too short convalescent period, [illegible]

hypertrophy, and why the hypertrophy should result in dysfunction, has never been satisfactorily explained There may or may not be a soft to loud systolic murmur best heard at the apex, but it is important to bear in mind that the mitral insufficiency is the result, and not the cause, of the myocardial insufficiency. This cardiac enlargement would seem to mark the beginning of a train of events that practically always ends in cardiac decompensation (c) Relatively uncommon are the patients with true chronic myocarditis At autopsy there may be found small foci of perivascular infiltration with lymphocytes and plasma cells, or, far less frequently, a focal or a widespread fibrosis with definite evidence of injury to the muscle fibers These chronic myocarditis cases are said to be indistinguishable clinically from those, above described, in which there is hypertrophy and no other change

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Myocardial Fatigue.—The practitioner who will assure patients with simple myocardial "fatigue," those described in group (a), that they have no heart disease and are sure to get well renders a real service to mankind, for these patients form a large class of chronic invalids who burden their friends with their "weak" hearts, and all because an incorrect diagnosis was made in the beginning Rest and reassurance, with a gradual return to full physical activity, is all that is needed in these cases; indeed, their easy curability is the chief mark by which they may be distinguished from cases of neurocirculatory asthenia, previously discussed. Christian said that these hearts, which are normal in size, sounds and function, offer the striking example of when digitalis should not be used, not that it is harmful but because it is not beneficial. Yet many of these patients are found to be entirely dependent upon daily doses of [illegible]

m [illegible]

in [illegible]

effect is being obtained

Hypertrophy and Chronic Myocarditis.—These cases, those described in

(b) and (c) above, are said often to present very considerable diagnostic diffi-

substantially supported in recent years by the observations of Gavey and Parkinson (1940), Wood (1940) and Larson and Hallock (1940). For example, Gavey and Parkinson compared the drug's action in sixty-five cases of decompensation with normal rhythm and thirty cases with auricular fibrillation: 60 per cent beneficial results were obtained in the former and 70 per cent in the latter cases. Wood obtained a beneficial effect in 90 per cent, and Larson and Hallock in 70 per cent, of their smaller series of regular rhythm cases. For the details of digitalis therapy the discussion of congestive heart failure must be read

CONGESTIVE HEART FAILURE

This is the state of broken compensation in which the heart is no longer able to perform the amount of work necessary if the body as a whole is to maintain a condition of normal activity. When first seen, if the decompensation is severe, the patient is in bed, usually propped up on several pillows,
nounced symp-
r may not be
of the lower
fluid in the
nd the urine
he lung bases
and congestive cough and even hemoptysis; sometimes cardiac asthma" and complaint of cardiac pain Slight fever is not at all infrequent even in the absence of infectious processes.

When primary left ventricular failure has persisted for a time the right ventricle not infrequently participates in the failure also and the picture is of the rather conglomerate sort roughly sketched above, but primary left ventricular failure alone presents quite characteristic symptoms when it occurs as
... excessive strain upon the left ventricle or deficiency in its contrac-
cular disease, in
oronary arterio-
ype of pain and
frequent attacks of one or another sort of arrhythmia are the outstanding features And then these patients are very likely to develop attacks of paroxysmal dyspnea that are frequently provoked in the night by bad dreams, or by an orthopneic patient slipping off his pillows, or perhaps as a result of distention of the abdomen from overeating, not infrequently such attacks eventuate in pulmonary edema. Oftentimes left ventricular failure begins slowly over a period of years and many patients who would profit by treatment for heart failure in its early stages merely complain of discomfort in bed at night unless propped up on several pillows, or a chronic bothersome cough, or some degree of effort angina, or some type of arrhythmia, and are treated merely for these single symptoms Wheeler and White (1945) called attention to the fact that insomnia alone as a presenting symptom of left ventricular failure, which may be easily ascribed to some other cause, is often overlooked

There is another sort of left ventricular failure that occurs very suddenly as a result of massive myocardial infarction, but the symptoms which quickly supervene are those of peripheral circulatory failure and the treatment is that for shock and therefore does not concern us at this time

In primary right ventricular failure, which is often in association with some obstructive situation or with mitral or congenital heart disease, dependent edema and signs and symptoms of engorgement of the abdominal organs and secondary congestive respiratory symptoms are usually the matters chiefly attracting the attention of the examiner. The right ventricle decompensates much more readily than the left but on the other hand it recompensates much more quickly and more frequently; by and large then the prognosis is much better in right than in left ventricular failure.

THERAPY

Rest.—Rest in bed is often self-imposed in cases of severe failure, though it is astonishing how long individuals of indomitable will are sometimes able to keep on their feet; it is certainly desirable in initiating treatment in severe

by being sent to bed, for the factors of arrhythmia, edema and congestion, and so on, are grave perpetuators of the broken-down state, but it does mean that, other things being equal, the severely decompensated patient who takes to his bed early and rests while he is in it usually has the best chance of recovery. However, as Levin (1940) pointed out, there are instances in which putting the patient to bed may cause a shift of some of the fluid from the dependent extremities, where it is relatively harmless, into the lungs, with the possibility of establishing serious congestion there before digitalis can begin moving the fluid to the kidneys. Harrison (1944) would allow the patient with congestive heart failure out of bed for several hours a day as soon as severe dyspnea at rest has subsided Dock (1947) said that he encourages early ambulation and sitting up at mealtime but also advises the patient to lie as flat as possible for as much of the day as he can in comfort. He feels that the erect posture long maintained leads to salt retention even in normal persons and predisposes cardiacs to nocturnal dyspnea. Gold (1944) has said that the diuretic effect of rest in bed is very considerable in many instances. Dock's opinion is that rest in the middle of the day and again before the evening meal is advisable in all chronic cardiacs to effect redistribution of the blood and a maximal basal cardiac output at more frequent intervals than occurs when people are up all day. However, he felt that the salt-retaining mechanism is not stimulated by sitting or standing for a short while and that early in recovery short periods spent in a chair improve the physical condition, minimize the risk of phlebothrombosis, and seem not to retard recovery or diuresis. The study of Burch (1946) of the importance of insuring a cool and comfortable atmosphere to avoid excitation of the thermal regulatory mechanism which would involve the cardiovascular system in an increased amount of work, indicated a possibly greater need for air conditioning in medical wards accommodating patients with heart disease than has heretofore been realized.

Diet and Fluids.—A good many years ago Allen, and indeed a number of other workers long before his time, urged the importance of a restriction of

salt in the diet, but the first practical application of this matter to attrac general attention was that of Schroeder (1941), who showed that if the in take of salt was restricted the intake of water could be raised considerabl without causing the formation of edema in patients with congestive failure This was just the sort of thing that Schemm had been saying for a numbe of years, but actually it is only quite recently that there has come abou general acceptance of this dietetic approach to the treatment of failure. It seems apparent that the reason for hesitancy has been that in the past our concept of the events in congestive failure has been that there occurred first heart failure, which led to an increase in venous pressure, which led to elevated capillary hydrostatic pressure, which eventuated in edema. Recently, however, Warren and Stead (1944) have postulated quite another sequence of events, namely, first, heart failure, second, diminished renal excretion of sodium and water, third, increased blood volume and edema, and finally, elevated venous pressure I think the consensus among cardiologists at the present time is that a true picture has not yet been painted, but certainly the newer approach, which stresses a reduction in sodium chloride intake to the practically irreducible minimum with the simultaneous permission of a large water intake, or even at times the moderate forcing of fluids, is yielding fine practical results and is being very widely applied. A recent representative report of the results of this sort of dieting has come out of White's Clinic at the Massachusetts General Hospital in the paper of Wheeler *et al.* (1947). This group chose fifty patients with congestive heart failure of all types, the patients being selected in general because previous therapy had been unsatisfactory, *i.e.*, dyspnea and edema had not been controlled or mercurial diuretics had been required at distressingly frequent intervals. Of the thirty-five patients who faithfully followed the diet and in whom the results could be fairly evaluated, thirteen did not show improvement while twenty-two did improve, ten of this latter group showing great benefit; in no instance was the patient made worse by the therapy.

Acid-Ash Salt-Poor Diet.—It is said that the average diet without salt restriction contains 6 to 15 gm. of salt per day, that without salt added at the table it contains 4 to 7 gm., that without salt added either in cooking or at the table it contains 3 to 4 gm.; and that with the careful choosing of foods because of their low salt content it may contain as little as 1.5 to 2.0 gm. Of course the latter will no longer be an "average" diet but it will be a completely sustaining one. In Table 24 will be found a simplified form of diet that requires no weighing of foods or concern with protein, carbohydrate or fat proportions and is easy to employ. The construction of such a diet rests upon three facts: (a) that sodium, particularly sodium chloride, is

products

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Dieting of this sort is being very much employed nowadays and with very excellent results, but it is universally found that the patients quickly tire of these diets and complain of the flat taste. Of course ammonium or potassium chloride may be used as substitutes for sodium chloride, but they are not as satisfying to the patient as might be wished. The reason that potassium chloride does not increase edema, and indeed may even promote the loss of edema fluid, is that sodium cannot pass through cell membranes and therefore holds water out in the intercellular spaces in order to maintain

osmotic equilibrium, whereas potassium diffuses into the tissue cells and hence does not contribute to the accumulation of extracellular fluid; but potassium being given in excess in this way may form potassium chloride, and a consequent electrolyte readjustment takes place with the elimination of sodium chloride and water in the urine A great contribution would be made by someone who would provide a satisfactory substitute for salt to flavor food. Schemm (1947), while not denying the value of the low sodium feature of this new type of dieting, still insists that increased water intake

TABLE 24.—ACID-ASH SALT-POOR DIET WITH UNRESTRICTED CALORIES
(MODIFIED FROM SCHEMM)

A Unrestricted Foods (from which at least two or three servings should be taken for any one meal)
- Eggs—Two may be substituted for one meat serving
- Meats—Any fresh meat, fish or chicken, one serving daily
- Bread—Whole wheat bread without salt or raisins
- Cereal—Puffed rice, puffed wheat, shredded wheat or any hot cereal cooked without salt
- Macaroni, spaghetti, rice, corn, cooked and served without salt or sauce
- Fruit—Prunes, plums, cranberries

B Restricted Foods
- Vegetables—Two small servings daily of any vegetable except parsnips, lima beans, rhubarb, chard and spinach, which are forbidden; use fresh or frozen vegetables or those canned without salt
- Fruit—One serving of fruit or fruit juice daily except raisins and dates, which are forbidden
- Milk and Milk Products—Two cups daily, one-quarter cup cream daily, unsalted cottage cheese substituted for meat

C. Other Foods
- Soup—May combine allowed vegetables with milk allowance or with salt-free broth
- Desserts—Plain jello or pudding made from allowed eggs, milk, bread, corn starch, junket (no cake or cookies)
- Beverages—One cup of coffee or tea at each meal
- Neutral Foods (which may be taken in any quantity) —Sugar, butter, salad oil, clear sugar candies

D Precautions.
- (1) No salt or soda to be used in cooking or at the table, small amounts of ammonium chloride may be used as a salt substitute
- (2) Use unsalted sweet butter or butter washed free from salt, unsalted bread, unsalted salad dressings
- (3) Eat no salted appetizers or salted foods such as nuts, potato chips, sardines, olives, pickles, relishes, no cheese except unsalted cottage cheese, no smoked or salted meats or fish such as canned salmon or tuna, no bacon (unless parboiled), ham, lunch meats, sausage, salt pork.
- (4) For "gas" or "indigestion" do not use sodium bicarbonate or any alkali powders or tablets (such as "Tums," etc), use only calcium carbonate obtained on prescription from physician if needed Avoid the notably gassy foods such as the cabbage family, turnips, rutabagas, peppers, radishes, onions, spices, greasy fried foods and pork

is of at least equal value and advises that where possible the patient be pushed to take considerable amounts of fluid He says that he has had cases in which the edema resisted the sharpest sodium restriction, and a good excess of acid ash in the diet, but cleared promptly when the water intake was increased to five or six liters daily. Leevy *et al.* (1946) published an interesting study of 122 patients with congestive failure, undertaking specifically to evaluate the relative merits of restricting fluids, allowing fluids *ad libitum*, and forcing fluids Of thirty-six patients observed on restricted fluids, 27.7 per cent complained of thirst, and 13.6 per cent discontinued restriction

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been completely confirmed and have not been translated into terms of practicability for the general practitioner, i e , manufacturers have not made available preparations of digitalis leaf standardized in terms of potency in man It would therefore seem that the practitioner today is best advised to follow one of two courses. either (a) to use a preparation of digitalis leaf obtained from one firm of manufacturers and employed by him in a routine fashion consistently with his experience of what he can accomplish with that leaf preparation; or (b) to use one of the newer crystalline glycosides obtained from digitalis that do not have to be bioassayed because they are pure chemical substances. The three such preparations available are. (a) lanatoside C, obtained from *Digitalis lanata;* (b) digoxin, also obtained from *D lanata;* and (c) digitoxin, obtained from *D. purpurea*, the older and more familiar form of foxglove which comprises the official U.S P. leaf

A great deal of clinical work has been done in comparing the above three agents, all of which are acceptable and valuable drugs with which to digitalize the patient. However, were I to offer here a fair comparison on the basis of all of this work I should fill my pages with an amount of material that would merely leave the reader confused and would not be of very practical service to him. Therefore, I shall be obliged to ask him to be content with the simple statement that in my opinion, which is of course merely an arm-chair reflection of a careful study of the work of those who have competently passed upon the matter at the bedside, it has been shown that digitoxin is the most suitable agent of the three for the rapid accomplishment and satisfactory maintenance

ously stated, this glycoside is practically 100 per cent absorbed from the

because of thirst; Leevy *et al.* felt that restriction of fluids may lead to dehydration with disorientation. On fluids *ad* [illegible] tient was found to consume approximately [illegible] 1800 cc. daily during the winter and 2200 [illegible] effects in any instance; these patients were much more comfortable than those in the preceding group. Of thirty-eight patients observed on forced [illegible]

easily with digitalis and the diuretics and indeed in some instances without the diuretics entirely.

Herrmann (1946) found slightly but definitely subnormal albumin levels [illegible]

rise to normal levels and suggested that the lag may be due to liver dysfunction. He concluded that high protein as well as acid-ash low-salt dieting is indicated in the treatment of congestive failure and edema.

Digitalis Indications and Effects.—The response to digitalis of a decompensated heart with auricular fibrillation is very spectacular. The pulse is decreased in rate and increased in volume; diuresis is established and edema decreases; dyspnea and cyanosis diminish—in short, compensation is reestablished and the patient's life is saved. In nonfibrillating cases, of the sort earlier described as "chronic nonvalvular heart disease," the reduction in rate is not so pronounced because the increase has not been so great, but the other evidences of powerful action are shown. The study of Blumgart and Altschule (1939) indicated that digitalis, in somewhat reduced dosage, may be safely employed for the correction of congestive failure in the presence of partial heart block. Erickson and Fahr (1945) placed a group of patients with clinically compensated but organically diseased hearts on maintenance digitalis [illegible] heart is not [illegible]

observed for a long time before it could be decided whether the life histories and span of such patients differ from those in whom digitalis is used only after the onset of heart failure.

Digitalis restores compensation probably principally through its local effects upon the heart, but it does not through its own action correct auricular fibrillation; however, the notion that it fixes (establishes more firmly) such fibrillation seems to be unfounded, for patients have been seen to revert to normal rhythm while taking the drug.

[illegible] In the U.S.P. XIII, which appeared in [illegible] t of digitalis represents the [illegible] Reference Standard Powder, [illegible] actitioner because the leaves from which the reference powder was made were of such high potency that

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two glycosidal preparations.

But another digitalis preparation is required by the practitioner, namely, a drug for intravenous administration when the rare case is encountered in which

usly stated, this glycoside is practically 100 per cent absorbed from the

intestine. Therefore it seems only natural to turn to the agent that experience has shown to be perhaps just a little more rapid in its action than any of the others, namely ouabain.

Finally, there is a situation in which one may have to go outside this group of three preparations—digitalis leaf, digitoxin and ouabain—for an acceptable agent, namely *instances in which congestive vomiting is very severe in the*

digitan may be given intramuscularly in dosage recommended on the ampule, for the pure digitalis glycosides are much too irritant for subcutaneous injection

other of the following circumstances: (a) if the economics of the situ-ation are of importance since digitoxin is more expensive than the leaf from which it is derived, and (b) in those instances in which it is advisable to switch a patient from one product to the other for psychological reasons.

(3) To have as his emergency preparation in the rare instances in which *intravenous injection is needed the compound ouabain.*

(4) To employ one of the older glycosidal mixtures when intramuscular *injection seems unavoidable.*

In what follows I shall attempt to describe as simply as possible the methods of using the three preparations, digitoxin, digitalis leaf and ouabain.

solution. Despite the fact that digitoxin is a crystalline substance it is possible that these various preparations of it may differ very slightly in potency—

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(1944), subsequently confirmed by many other observers, found that a single *oral dose of six of the 0.2 mg. tablets (or 6 cc. intravenously of the ampule preparation if the patient is vomiting severely) will achieve control of the cardiac failure and that thereafter the daily administration of 0.2 mg. suffices for maintenance.* Administering digitoxin in this way, digitalization is achieved in a period of six to ten hours, but it must be fully understood that such dosage as the above can be employed only in the patient who has not had any digitalis for the preceding ten days at least. Gold (1945) of course admitted that there are tolerant patients who require more than 1.2 mg. of digitoxin for full therapeutic effects and that in such instances it may be necessary after six to ten hours to administer *another 0.2 mg. in order to obtain full digitalization, thereafter returning to the 0.2 mg. at twenty-four hour intervals for maintenance.* He also said that in a few patients it is necessary to reduce the maintenance dose to 0.1 mg. or occasionally to increase it to 0.3 mg. Full digitalization through the use of digitoxin by mouth

is accomplished practically without causing any nausea or vomiting from local irritant action. Katz and Wise (1945), in confirming the findings of Gold and his associates, felt that as a general rule it would perhaps be preferable to divide the 1.2 mg. dosage as follows: 0.8 mg. at once, followed by 0.4 mg. in six to eight hours, and by such subsequent doses as might be necessary to attain the desired effects. In regard to supplementing the initial digitalizing dose of 1.2 mg., Freedberg and Zoll (1946) pointed out that the desirability of such procedure will depend upon whether the patient has auricular fibrillation with a rapid ventricular rate, auricular fibrillation with a slow ventricular rate, or normal rhythm. Their opinion was that in the presence of auricular fibrillation with a rapid ventricular rate, 0.2 to 0.4 mg. should be administered at intervals of six to eight hours after the initial 1.2 mg. dose until the ventricular rate reaches approximately 70, and that it is not necessary in such patients to carry them to the point of minor toxicity, but to complete full digitalization in patients with auricular fibrillation and a slow ventricular rate or with normal rhythm, additional doses of 0.4 mg. must be administered at intervals of six to eight hours until the earliest toxic symptoms are produced. In their experience the subsequent maintenance dosage has varied from 0.1 to 0.4 mg. daily, and in addition they have occasionally found it necessary to redigitalize patients with congestive failure at intervals of four to six months despite the fact that they have been on what it seemed should have been adequate maintenance dosage.

Digitalis Leaf.—Digitalis leaf is official in the U.S.P. XIII (1947) in the powdered form and in capsules and tablets of 1½ grain (0.1 gm.). Ample experience through the years has established the fact that in most cases of congestive failure in which digitalis has not been administered during the preceding ten days to two weeks, full digitalization may be accomplished by giving a total of 20 to 25 grains (1.2 to 1.5 gm.) of the leaf, and that subsequent control on a maintenance basis can be achieved with the administration of 1½ to 3 grains (0.1 to 0.2 gm.) in a single daily dose. A possibly useful thing to remember is that the relationship of the dosage of digitoxin to the dosage of the leaf is 1:1000. But one cannot achieve digitalization rapidly through the use of digitalis leaf orally in one large dose, as is the case with digitoxin, for the reason that, while perhaps only 20 per cent or slightly more of the total dose of digitalis is absorbed from the gastro-intestinal tract, all of it that is placed therein is irritant and therefore a large number of patients, about one out of five according to Gold (1946), will develop nausea and vomiting within the first hour due to the local effect of the large dose. Therefore one compromises and gives such amounts as will be borne by the patient and must be satisfied with achieving digitalization in thirty-six to seventy-two hours. Many schemes of digitalization with the leaf by mouth are in use and have been published; probably that most usually employed is the one advocated by Freedberg and Zoll (1946) in their review of this whole subject, namely the giving of 4½ grains (0.3 gm.), which would be three of the U.S.P. tablets or capsules, three times daily for the first day and 1½ grains (0.1 gm.), or one tablet or capsule, three times daily thereafter until the optimal therapeutic effect or symptoms of minor toxicity appear. When full digitalization is achieved, one may discontinue for a day if it is felt desirable and then place the patient on a daily maintenance dose of 1½ to 3 grains (0.1 to 0.2 gm.) as indicated. In the case of the leaf as with digitoxin, it is advisable always to use the preparation of the same manufacturer.

kg.): give 1½ grains (0.1 gm.) as test dose; two hours later, 3 grains (0.2 gm.); eight hours later, 3 grains again; and eight hours thereafter, 1½ grains. If not digitalized at the end of the twentieth hour, continue 1½-grain doses every six hours for one or two more doses provided there are no signs of toxicity, and then place the child on maintenance dosage. However, Stewart (1942), of the Cornell Group, said his observations with Cohn were that body weight has nothing to do with the amount of digitalis required for therapeutic effect and that he therefore gives the same amount to children as to adults; questioned further with regard to this attitude he stated that the youngest patient he had so treated was a four-year-old child with auricular fibrillation to whom full adult dosage was given and therapeutic effect achieved without the induction of nausea and vomiting. The efficacy of digitalis in rheumatic heart disease is discussed in Rheumatic Fever. If it is desired to digitalize more slowly, give 1½ grains (0.1 gm.) three times daily at six-hour intervals (8, 2 and 8 o'clock, or 10, 4 and 10 o'clock) for three days; fourth day, a dose in the morning and if necessary at night; thereafter maintenance dosage, which would probably be 5/6 grain (50 mg.) daily, six days a week.

Ouabain Intravenously.—Crystalline ouabain, the glycoside obtained from *Strophanthus gratus*, is the preferred preparation in America; in England *S. kombé* is used and *S. emini* has been investigated. The commercial ampules contain 0.25 mg. per cc. in buffered isotonic solution in hard glass, under which circumstances the drug is stable. Wyckoff and Goldring worked out the

minutes in average cases and full effect in about an hour. Most conservative men nowadays give only one dose or at most do not repeat the dose in less than twenty-four hours, but Wyckoff felt that in the presence of marked auricular fibrillation, where therapeutic effect can be easily noted, several subsequent doses of 1/600 grain (0.1 mg.) may be used at half-hour intervals after the initial large dose, Eggleston (1940) preferred one- to two-hour intervals if

stances and how much of the drug to give have been important and not entirely

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grains, 0.6 gm. for weights between 125 and 175 pounds; 13 grains, 0.8 gm., for weights above 175 pounds); (b) no further medication for twenty-four hours;

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familiarize himself with *all* the signs of toxic action and not be content to recognize merely the most familiar ones, such as vomiting, drowsiness and excessive slowing of rate. The following is the list, arranged for convenience in memorizing:

Gastro-intestinal	Nausea, loss of appetite, vomiting, diarrhea.
Circulatory	Extrasystoles, coupled rhythm, ventricular tachycardia, partial or complete heart block, simulation of any of the other spontaneous arrhythmias, diminution in secretion of urine, cold extremities.
Nervous	Headache, drowsiness, mental confusion, visual disturbances

lation of the vomiting reflex may be succeeded by depression of the same, so that to rely greatly upon nausea and vomiting as measures of the degree of

this matter is discussed in Rheumatic Fever.

Against a background of animal experimentation of other workers, Massie *et al* (1944) studied the effect of digitalis on the blood coagulation time in man, twenty-four patients being employed, some with and some without heart

coagulability of the whole blood in ten patients during oral digitalis therapy And there the matter stands.

In extremely rare instances, urticarial or scarlatinal rashes, asthma, angioneurotic edema, or some other allergic reaction to digitalis is observed

Excretion of digitalis in the milk has not been demonstrated and almost certainly does not occur, there is therefore probably no danger to the infant if the nursing mother is digitalized, but even so I should think that a bit of extra watchfulness would not be amiss.

necessary to relieve them quickly. In a *Cornell Therapeutic Conference*, in 1943, Eggleston discussed the matter very thoroughly. The essentials of the therapy advocated by him may be stated as follows: (a) The patient is placed in a sitting position in bed with the legs lowered if that is possible, which is of course not usually the case in the home; indeed one can often do little more than raise the head. (b) Morphine sulfate is then given in a minimal dose of ¼ grain (15 mg.) to effect relief of psychic distress; Eggleston did not favor the concomitant use of atropine unless in quite larger doses than those usually employed, and stated that he used it very little. (c) As soon as possible after

by aminophylline in these cases. (d) Then Eggleston would bleed the patient, withdrawing at least 500 cc.; if this is not feasible he resorts to so-called bloodless phlebotomy, the application of tourniquets so as to constrict the four limbs close to the trunk tightly enough to prevent venous return. (e) Oxygen is administered if and as soon as feasible. At the same Conference, Wolf (1943) presented the advantages of positive pressure oxygen therapy as developed largely by Barach. It is felt that during an attack of pulmonary edema intrathoracic and intrapulmonary pressure becomes lower as the result of obstruction to inspiration opposed to increased inspiratory effort on the part of the patient; positive pressure therapy would tend to relieve the negative pressure and thus reduce the return flow of blood to the congested lungs and the failing left ventricle. Oxygen under pressure also increases the oxygenation of the capillaries and thus opposes an increase in capillary permeability and the withdrawal of blood from the pulmonary capillaries into the alveolae in the state of negative intrapulmonary pressure obtaining in these patients. A further *advantage of the pressure therapy is that by raising the intra-alveolar pressure* it tends to inhibit the formation and to facilitate the absorption of the transudate.

Of course these patients are to be placed upon digitalis and the mercurial diuretics, *the latter being of particular value, as pointed out by* Modell (1943), since by the elimination of depots of fluid in the body that are not clinically apparent they tend to prevent redistribution of the water at night and to prevent the development of paroxysmal nocturnal dyspnea; as a ... even when no

the best possible state.

Diuretics.—Not only are the diuretics of immense value in cases of left ventricular failure, as discussed above, but where edema is marked, as it ... valvular ... nt is ... (see ... ab-

dominal cavity and subcutaneous tissues seems to be equally ... d by the diuretics; that in the pleural cavity much less so. Lack of distensibility

of the thoracic cage makes the latter much more disturbing to the patient also. It is the practice of many physicians to remove this fluid by thoracocentesis as soon as any considerable dullness is detected on chest percussion Volini and Levitt (1940) found that cerebrospinal fluid pressure is reduced by the effective employment of diuretic drugs Levine (1940) found that in some instances effective diuresis is obtained only after abdominal paracentesis has released pressure on the renal vessels In a few instances of resistant dependent edema, Southey tubes may be of value.

Mercuhydrin and Mercupurin (Mercuzanthin).—These mercury compounds containing theophylline are the most effective diuretics so far developed. Formerly the mercurials were given only intravenously but now that they have the xanthine mixed with them they may also be given intramuscularly. It is customary to use the acid-forming salts (see below) with them since it is the opinion of most men that greater diuresis is thus induced, but it seems to be Gold's opinion that there is not much advantage in the combined therapy. Modell *et al.* (1945) used mercuhydrin in a study employing ninety-two patients, in forty-three of whom the drug was compared with mercupurin They found that the diuretic responses to the two drugs were indistinguishable when they were given either intramuscularly or intravenously, that as shown by urine examinations and blood nonprotein nitrogen values neither of them produced renal injury after weekly injections for periods of three months, and that mercuhydrin was less irritant than mercupurin by intramuscular injection. In a subsequent study (1946) they reported that the best response of most patients to mercuhydrin is obtained in a dosage range between 0 5 and 1 5 cc at weekly intervals Gold (1946) said that accumulation of these mercurial drugs is negligible because their elimination is rapid, a dose of 1 to 2 cc being eliminated in less than twenty-four hours. He found it advisable to begin with a small trial dose of 0 5 cc and if this produces no untoward effect to increase the dose to 1 or 2 cc as necessary In his opinion the most satisfactory plan is to administer one dose every day, the patient being weighed before each dose and daily dosage being continued until a "dry weight" (*i e*, the point at which a daily injection no longer produces a loss of weight) is reached, at which time the interval between doses may be prolonged to every two, three, four or more days as indicated by the weight record

Chapman and Shaffer (1947) reported that in patients with congestive failure to whom they gave mercuhydrin in doses of 2 cc. intravenously they felt they had obtained better results through the mixture with it of 500 mg. of ascorbic acid than would have been obtained without it This group of investigators had previously reported similar results from the use of ascorbic acid with mercupurin, but these were very small-scale studies and not controlled and certainly considerably more work will have to be done before one can be justified in feeling that there is any place for ascorbic acid here

In the Department of Therapeutics, New York University College of Medicine, a thorough study is being made of the oral method of administering mercupurin, using tablets containing 120 mg. as compared with the 135 mg. per cc of the parenteral solution. Employing five tablets as a single dose in thirty-four trials in twenty-four patients, Batterman *et al.* (1946) reported that a satisfactory response had been obtained in 58 per cent of the trials; diuresis usually began within four to twelve hours and with few exceptions was completed in less than twenty-four hours. But they found that

these results did not compare favorably with those obtained from intravenous administration. In their multiple dose method one to three tablets three times daily for a period of two to five days constituted a trial, thirty-nine such courses being given to twenty-nine patients, and a satisfactory response being obtained in 67 per cent of the trials. Diuresis usually developed slowly when the drug was given in this way and in many patients did not reach its peak before forty-eight hours, nevertheless it was said that the total diuretic response frequently approached that achieved with the intravenous preparation. It was felt that this is not the ideal method for patients in whom rapid removal of edema fluid is desired, but that for those who do not require emergency measures, for those who should have the edema fluid removed gradually, and for those who cannot be given the diuretic parenterally, it is the ideal method. Batterman *et al.* emphasized in connection with this dosage that their relatively poor results (only 67 per cent of successes) were undoubtedly contributed to by the fact that in some instances they deliberately

an oral diuretic is used. Toxicity with this method was found to be of little consequence in hospitalized patients, mild gastro-intestinal irritation of a transient nature being observed in only two of twenty-nine individuals, but gastro-intestinal symptoms were noted in six of thirteen patients treated on an ambulatory basis. The third, or daily dose method, of Batterman *et al.* consisted in a study of thirty trials in twenty-six hospitalized patients and thirty-one trials in eighteen ambulatory patients, all of these patients being in progressively severe congestive failure no longer responding to a maintenance dose of digitalis, and all with few exceptions having previously received frequent injections of mercupurin intravenously. The twenty-six hospitalized patients received two tablets in an undivided dose for periods of seven to forty-one days, the ambulatory patients from one to two tablets daily for periods of one to forty-nine weeks, patients in both groups being observed with and without the additional administration of ammonium chloride The patients who responded to the daily dose required from four to fourteen days of continuous therapy before the medication became effective, and in some instances it seemed advisable to continue intravenous dosage of 1 cc until the orally administered drug became effective Of the twenty-six hospitalized patients who had been previously uncontrolled, complete removal of the edema and alleviation of acute symptoms were obtained in fifteen and very considerable improvement in four; effective diuresis was therefore considered to have been attained in 73 per cent of the hospitalized patients. In the ambulatory group such results were said to have been attained in 77 per cent of the patients Toxicity associated with the daily dose

cent of the ambulatory patients Gastro-intestinal symptoms, associated with increasing albuminuria, occurred in three instances, these being signs of mercurialism in patients who had previously presented evidence of kidney disease; in one of these three patients the symptoms were associated with severe gingivitis and elevation of nonprotein nitrogen, all of these manifestations subsiding when the diuretic was discontinued. The experience of

this group of observers with a few other patients who presented albuminuria while on the oral mercurial diuretic, but no further symptoms of mercurialism, led them to believe that albuminuria itself does not contraindicate the continuation of the use of mercurial diuretics They said, however, that it has become their policy after the maximum effect of the oral diuretic has been achieved to allow the patient a rest period of a week and then to continue the diuretic for one month, short rest periods thereafter being given between monthly courses But since two patients not of this albuminuria group presented considerable elevations in nonprotein nitrogen associated with the other signs of uremia, Batterman *et al.* concluded that the oral mercurial should not be used in any patient who presents impaired kidney function.

In summarizing their findings with the above-described oral method of [illegible]

a mercurial diuretic, reaccumulated their edema or experienced a recurrence of acute symptoms. They said that in such patients the oral diuretic will remove all signs and symptoms of failure, making it possible either to dispense with the intravenous preparation or to decrease the number of injections required However, Gold (1946) said that he had not often been able to employ oral tablets of the mercurial diuretics with satisfaction, small doses being rarely effective and effective doses soon causing gastro-intestinal upsets. But I do not know how extensive his experience with the oral method has been.

It seems to be the consensus that mercurin or salyrgan-theophylline suppositories do not very dependably induce diuresis and occasionally cause local discomfort and burning

Of course the mercurial diuretics can give rise to the type of poisoning characteristic of mercury itself Modell (1942) warned that the organic mercurials are excreted almost quantitatively in the urine only so long as there is good diuresis and that as diuresis falls off special caution must be taken when using these drugs since mercury retention may occur in the body But Gold (1944) did not seem to be impressed by Modell's contention since he said he thought that if there is anywhere near a normal urine excretion, even though no diuresis results from the use of the drug, there is virtually no danger of accumulation of mercury with the usual plans of administration. The number of recorded authenticated cases of mercury poisoning consequent upon the use of mercurial diuretics is very small, still, attention should be drawn to the case of Waife and Pratt (1946), an individual with rheumatic heart disease and cardiac decompensation, who developed fatal anuria after six months of mercupurin injections and whose death was ascribed to mercurial intoxication since the postmortem examination revealed nephrosis, hemorrhage in the ileum and colon, and focal areas of necrosis and hemorrhage in the liver. A similar case was reported in one of the clinicopathological conferences at the Massachusetts General Hospital in 1945 (see Mallory *et al* in Bibliography) What has caused the profession more concern than mercurialism is the fact that these drugs like any other potent agents occasionally give rise to idiosyncratic reactions in susceptible individuals Sometimes these reactions seem to be related to the particular compound used because another preparation can subsequently be employed with safety, but more often it would seem that they have been direct re-

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actions to the mercury itself. Some of these reactions have been of a cutaneous nature, in others there have been chills or fever, or in others a state of shock, collapse, and urinary suppression, and there have been some deaths. But the number of deaths or even of severe reactions has been far below that which would indicate that these diuretic agents are not safe for routine employment. De Graff and Nadler (1942), reviewing the entire subject, stated that at Bellevue Hospital approximately 6000 injections, most of them intravenous, of mercurial diuretics are given every year, and that since 1934 they had known of no serious toxic reaction or death ascribable to these drugs. Friedenson (1944) reported the case of a young woman who died of far advanced rheumatic heart disease, after having received over a period of twelve years 627 injections of a mercurial diuretic with good diuretic response always, no reaction and no evidence of renal damage These findings were the same in the case of Wood and Livezey (1942) whose patient had been given 350 injections. Gold (1945) pointed out that the small number of fatalities had invariably been associated with intravenous administration of these drugs. He said furthermore that there should be no hesitation in using these compounds when a diuretic is necessary irrespective of the state of the kidney. Some of the reactions are the result of excessive diuresis, some patients developing no untoward symptoms when they lose ten pounds of edema fluid in one day while others develop marked weakness and cramps with an abrupt loss of as little as two or three pounds. Marshall (1947) reported evidence of tetany occurring on three occasions in a patient following the parenteral use of a mercurial diuretic and drew attention to the need for considering the mobilization and excretion of electrolytes other than the chlorides, particularly in patients who may have a border-line calcium deficiency. In his case the parenteral and oral administration of calcium in moderate doses relieved the tetany and did not induce deleterious effects though the patient was fully digitalized at the time. Ben-Asher (1946) made the point that because of the excessive dehydration that may follow diuresis and the loss of chlorides through the sweat glands, mercurial diuretics should not be given during a period of high environmental temperature. It is doubtful if there is any real justification for the belief that the hemodilution occasioned by the use of mercurial diuretics is so great as to contraindicate their use in an individual suffering from congestive failure superimposed upon coronary occlusion

Acid-Forming Salts.—The most effective of the acid-forming salts are ammonium chloride, ammonium nitrate and potassium nitrate; ammonium chloride is perhaps the one most used. Unfortunately all of these compounds are very irritating to the gastric mucosa [illegible] given in dosage of 90 to 150 grains (6–1[illegible] throughout the twenty-four hours. The f[illegible] prescriptions, containing 15 grains (1 gm.) of the drug per teaspoonful.

℞	Ammonium chloride	℥i	30 0
	Anise water	℥i	30 0
	Syrup glycyrrhiza to make	℥iv	120 0
	Label. 1 or more teaspoonfuls well diluted as directed		
℞	Potassium nitrate	℥i	30 0
	Syrup glycyrrhiza to make	℥iv	120 0
	Label. 1 or more teaspoonfuls well diluted as directed		

Gold (1944) stated his belief that the acid-forming salts are not very satisfactory when used alone because as soon as dosage is increased to a point where

their efficiency is fairly high they begin to behave like saline laxatives However, some individuals are able to take very large doses without being disturbed and they often obtain excellent diuresis

Decholin.—Modell and Gold (1945) studied the diuretic action of sodium dehydrocholate (decholin sodium) in comparison with mercupurin in thirty-two ambulatory cardiac patients. The decholin sodium was used in 20 per cent solution in doses of 10 cc. intravenously, taking two to three minutes for the injection. Most of the patients received four such doses either alone or in combination with mercupurin, the two drugs being mixed in the same syringe when they were given together, when used alone mercupurin was also injected intravenously. As a result of 234 intravenous injections of mercupurin and 98 of decholin sodium, these observers concluded that 2 gm. of decholin sodium given together with 1 cc. of mercupurin can be expected to produce a diuretic effect similar to doubling the dose of mercupurin, but that patients resistant to the diuretic action of mercupurin are likely to be resistant to that of decholin as well

Xanthines —The following are probably average dosages to be administered [illegible]

intramuscular or intravenous administration, the latter to be performed very slowly Gold (1944) said that it is very unusual for him to be able to carry a patient along satisfactorily by means of any one of the xanthines orally; as soon as the dosage is raised sufficiently to give effective diuresis the patient develops so much trouble in the form of gastro-intestinal symptoms and nervousness as to make it impossible to continue He said that if the mercury injections become intolerable one will do better in resorting to the rectal suppository of salyrgan or mercurin than to expect as much from the xanthines. Batterman *et al* (1946) said that they had never been able to achieve with the oral xanthine preparations such results as they achieved with the oral mercurial diuretics.

Urea —Urea seems often to succeed as a diuretic where the xanthines fail; it is inexpensive and practically nontoxic, but if there is an associated nephritis it is well to check the blood urea nitrogen now and then to be sure that excessive retention is not taking place. But the drug is extremely disagreeable in taste and many people simply cannot take it for that reason. Usual dosage is about 30 cc of a 50 per cent solution of the urea stirred up in water or fruit juice three times a day. Wheeler (1942) said that many people find grape juice a particularly effective vehicle Or the agent may be prescribed in the following form, in which one teaspoonful will contain 15 grains (1 gm):

℞	Urea	℥i	30 0
	Acacia powder	℥iij	12 0
	Syrup of cinnamon to make	℥iv	120 0
	Label 1 or more teaspoonfuls well diluted as directed		

Quinidine.—[illegible]

shift from fibrillation to normal rhythm and back again. Stewart (1945) also said that he does not use the drug if there has been heart failure, and Pardee (1945) said he thinks it may be used only in a patient whose failure is cleared up and whose functional capacity has reached a high rating. It certainly seemed to be the consensus at the Cornell Therapeutic Clinic at which the matter was thoroughly discussed that, as expressed by Eggleston, in patients with the so-called fixed type of fibrillation quinidine is unnecessary, there are certain very real hazards in connection with its use, particularly the hazard of dislodging emboli from the intra-auricular thrombi, and that there is likelihood of only temporary benefit. Both Pardee and Stewart took the position, however, that in a patient who has been fibrillating for a year or so after the [illegible]

in which just such a patient was having repeated showers of emboli which were stopped when quinidine restored normal rhythm But Gold cited a case in answer in which a procedure had apparently brought about the patient's quick death from embolus. So there the matter stands so far as embolism is concerned. But Askey (1946) concluded from a study of the literature and his own experience that the principal hazard from the use of quinidine is sudden death and not the possibility of increasing the incidence of embolism. He felt, however, that though sudden death is a hazard in some of these cases, the increased risk at times may be justified owing to the risk of heart disease itself. Gold (1945) said that he thinks it a good plan to avoid the use of quinidine in a patient who has had large doses of digitalis.

Thiouracil.—There was a period some years ago during which it was rather popular to consider that the removal of the influence of the thyroid gland might prolong life in cases of congestive heart failure through a reduction of the total oxygen requirement of the body and a decrease in the work of the heart. Total thyroidectomy was employed to some extent during this period [illegible]

treatment with bed rest, digitalis and mercurial diuretics. This innovation may come to nothing; yet now that we have propylthiouracil with its relatively low toxicity it is not impossible that future studies will discover some merit in the approach

ANGINA PECTORIS

The attack of angina pectoris reflects a transitory period of undernourishment of a portion of the myocardium and is therefore really only a symptom of serious underlying cardiac disturbance rather than a disease *sui generis* In the series of 445 patients of White *et al.* (1943), 76 per cent died from cardiac causes There is no longer convincing evidence that the intellectual are any more frequently stricken than the working classes, but Amadeo's (1944) observation that the poverty-stricken, malnourished, chronically hookworm infected and hence severely anemic peasantry of Puerto Rico seldom exhibit the symptoms of angina pectoris is to me very interesting His postulation that in these anemic individuals a vast net of collateral anastomotic coronary vessels has been formed would certainly seem worthy of exhaustive investigation, for Gilbert (1945) emphasized, as Herrick had done many years before and many have done since, that even moderate anemia sometimes may be an accessory *cause* of anginal pain, though Cassidy in his Harveian oration (1946) felt that the anemia must exist in association with some degree of coronary atherosclerosis, for he had never even seen a severe anemia cause angina in a young subject, though he was aware that Hunter (1946) had described such cases The history of the seizure as described by the patient is usually very [illegible]

[illegible]

characterized also by one other conspicuous feature, the immobility of the patient, he may elect to stand or to sit bolt upright (he rarely reclines), but whatever his posture he retains it fixedly, rarely even emitting a groan despite his pain, until the attack has passed. The paroxysm may last only a few seconds or it may persist for several minutes, if it lasts more than one-quarter hour, the observer does well to suspect coronary occlusion White is said to have pointed out, according to Cassidy (1946), that in the first edition of his book on heart disease a sentence emphasizing the relationship between angina and stress was in italics, that in the second edition it appeared in [illegible]

[illegible]

stress is apparently associated provocatively with the seizures The standardized exercise tolerance test is frequently used as an aid to diagnosis

An exhaustive statistical study of the material at the Mayo Clinic was reported by Parker *et al* (1946), who showed that 88 per cent of the patients with angina were at the time of onset of symptoms in the fifth, sixth and seventh decades of life, and that the ratio of men to women was 4 3 to 1. The highest mortality rate occurred in the first year following establishment of the diagnosis of coronary arterial disease with angina pectoris, thereafter the mortality rate was less although it continued relentlessly yearly throughout time. The survival rates of women were greater than those of men. When corrected for deaths not due to angina pectoris, the five year survival rate of patients thirty to thirty-nine years of age was definitely shorter than when the disease manifested itself later in life Such associated conditions as cardiac

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with pain of variable degree but more often crushing than knifelike and accompanied frequently by a sense of impending death When the pain radiates it is nearly always into the left shoulder and down the left arm, but sometimes it extends up into the jaws also The paroxysm in its more severe form is characterized also by one other conspicuous feature, the immobility of the patient, he may elect to stand or to sit bolt upright (he rarely reclines), but whatever his posture he retains it fixedly, rarely even emitting a groan despite his pain, until the attack has passed. The paroxysm may last only a few seconds or it may persist for several minutes, if it lasts more than one-quarter hour, the observer does well to suspect coronary occlusion White is said to have pointed out, according to Cassidy (1946), that in the first edition of his book on heart disease a sentence emphasizing the relationship between angina and stress was in italics, that in the second edition it appeared in ordinary print, and that in the third edition it was deleted altogether Some patients experience most of their attacks at night in bed it is true, but nevertheless there are others in whom exposure to cold or emotional or physical stress is apparently associated provocatively with the seizures The standardized exercise tolerance test is frequently used as an aid to diagnosis

An exhaustive statistical study of the material at the Mayo Clinic was reported by Parker *et al* (1946), who showed that 88 per cent of the patients with angina were at the time of onset of symptoms in the fifth, sixth and seventh decades of life, and that the ratio of men to women was 4 3 to 1. The highest mortality rate occurred in the first year following establishment of the diagnosis of coronary arterial disease with angina pectoris; thereafter the mortality rate was less although it continued relentlessly yearly throughout time The survival rates of women were greater than those of men When corrected [illegible]

hypertrophy, well defined hypertension, previous cardiac infarction, congestive heart failure and significant electrocardiographic abnormalities were clearly related to a higher mortality rate and lower survival rates. Of the entire group of 3440 patients, including those with all of the complications that were encountered in the series, and irrespective of age at onset or of sex, there was a survival rate for the first *year after diagnosis* of 82 *per cent* (*but during the* first year from the time of the onset of symptoms the survival rate was 94 per cent). By the end of the second year after diagnosis the survival rate was only 73 per cent From year to year thereafter the survival curve indicated a rather constant mortality rate of approximately 10 per cent among the survivors

The first complete description of angina pectoris was that of Heberden before the Royal College of Physicians in London, in 1768.

IMMEDIATE RELIEF OF PAIN

Nitrites.—Amyl nitrite by inhalation often brings relief in thirty seconds to one minute; it may be conveniently carried on the person in the form of a box of the "pearls," one of which is crushed in the handkerchief for inhalation But the odor is often objectionable to the patient and others who may be nearby when the necessity to use the drug arises, relief is also not so certain as with nitroglycerin. This latter drug may be prescribed in 1/100 grain (0 6 mg.) ... less expensive than the pearls

patients, the tablets retain their effectiveness for at least four months. However, that tablets exposed to heat rapidly lost their clinical effectiveness means that they should not be kept near steam pipes, radiators, etc. The dose is 1 tablet, more or less, dissolved under the tongue, not swallowed; the full effect is more slowly achieved than with amyl nitrite—two to three minutes usually. While many patients have taken quite large doses of nitroglycerin with apparent impunity, a small number of pronounced reactions has been recorded: ... headache and palpitation, and con- ... e (1933) observed ... pointed out that ... in (0.15–0 3 mg.) ... he believed these small doses to be routinely as effective as the larger ... Christian advised many years ago that the patient be urged to remove the undissolved portion of the tablet as soon as relief is experienced.

Alcohol.—It is said that a stout drink of whiskey or brandy, or any hard liquor taken "neat" with very little water to "chase" it, may bring quick relief in the anginal attack, and that this measure is effective occasionally ... Stearns et al. (1946) actually gave alcohol a

without associated objective improvement, and a few patients were subjectively worse.

SUBSEQUENT THERAPY

The individual who has had an attack of coronary occlusion may also subsequently have anginal attacks, and since the measures employed in him are the same as those employed in an individual who has experienced angina pectoris but has not yet had an attack of occlusion, I am describing these measures all together here, leaving it to the reader's judgment to determine in given instances which measure is more particularly suited for his patient.

Mode of Life.—If the overworked, overworried, overwrought individual with coronary disease can be brought to relinquish in whole or in large part his professional or business affairs, and can be brought to adopt the mode of life of a person of indolent habit and independent means, and to model his temperament upon that of the cow; and can be induced to journey south in a leisurely fashion during the inclement months, going preferably to a spa; and can be reeducated to eat slowly of light foods in small amounts—that is to say, if all that is practically impossible for the average competing individual in a work-a-day world can be accomplished—then the patient may be said to have the best chance of prolonging his life I do not know of any well-substantiated evidence that altitudes of 10,000 or 12,000 feet, which is about the average ceiling of transport planes in this country, are harmful, though it would certainly seem wise for the individual whose anginal attacks occur on very slight exertion or even at rest to avoid flying altogether, just as indeed he should avoid strains of all sort Many physicians do not permit sexual intercourse; it seems to me that in a certain sort of individual the loss of this right might in itself provoke an attack.

Diet.—Full heavy meals and especially gas-forming foods are to be avoided. Articles of food not well borne must be discovered by the individual patient, indeed, having reached the age of most of these patients he has long known the things that disagree with him and needs only to eliminate these from his diet. Levy (1937) showed that coffee will induce cardiac pain in some individuals Hydrochloric acid with meals is helpful to some patients; carminatives after meals are not contraindicated (see Index for prescription). Gilbert (1945) laid great stress upon the fact that the patient should approach the taking of a meal in as calm and relaxed condition as possible, saying that a small dose of belladonna or phenobarbital or some other preparation with similar effect at mealtime is a great help

There are indications that obesity is a handicap More than half Goldsmith and Willius' (1937) series of 300 patients at the Mayo Clinic were overweight, in the series of eighty fatal cases of coronary disease in soldiers in the American Army, reported by French and Dock (1944), the most striking presumable predisposing factor was overweight, which was present in 91 per cent of the cases However, in reducing the weight of the victim of coronary disease, thyroid extract should definitely not be used

Tobacco and Alcohol.—It seems to me that there has been considerable misunderstanding of the report of White and Sharber (1934), who compared the past alcoh[illegible] and tobacco habits of 750 angina pectoris patients with 750 individuals w[illegible] They found no evidence that the use of either of these [illegible] role in the genesis of the malady, [illegible] ently aggravated or precipi[illegible] Many doctors are [illegible] prevent or to relieve them [illegible] that they can continue to [illegible] this evidence in their joy at finding

endangering their coronaries—perhaps it would have been better to use the word "surprise" instead of "joy" above, for most of us really suspected the

younger age groups. May I say that when or if I come down with coronary disease I shall stop smoking if I can and at once change my drink from beer, which distends the stomach, to hard liquor?

Nitrites.—The disagreeable effects of drugs of this group, occasionally seen when amyl nitrite or nitroglycerin is used for the relief of an attack of angina, are much more frequent accompaniments of the routine use of the longer-acting members, the tetranitrates and sodium nitrite. But in an individual who is having many anginal attacks during the twenty-four hours it is sometimes possible to lessen both their number and severity for a time at least by the use of these preparations, the result is said to be especially gratifying in those whose nocturnal attacks make the nights very miserable. Erythrityl tetranitrate and mannitol hexanitrate are available in 1/4 and 1/2 grain (15 and 30 mg.) tablets; the dose is 1/4 to 1 grain (15 to 60 mg.) every four to six hours. These salts are rather expensive. Sodium nitrite is cheaper but very irritating to the stomach. Many practitioners who formerly used the latter drug thought it more effective when combined with sodium or potassium iodide. The sodium nitrite dose is 1 to 3 grains (60 mg. to 0 2 gm) in tablets or capsules.

Xanthine Vasodilators.—Many physicians have thought these drugs helpful, though most patients are somewhat upset by them, the untoward effects are nausea and sometimes vomiting, a burning pain in the epigastrium or under the sternum, palpitation, dizziness, headache, "nervousness," and a few other minor complaints. The drugs of the group and their dosage are given in *Congestive Heart Failure*. Not only tolerance but also cross tolerance to these drugs seem to be acquired by an occasional patient; some men have the medication taken for four consecutive days of each week and omitted on three, and they alternate theobromine with a theophylline preparation The studies of Levy *et al.* (1941) pointed strongly toward the ability of aminophylline to postpone the appearance of pain; McMahon and Nussbaum (1940) concluded that favorable changes in the electrocardiogram often result from the intravenous administration of this drug. LeRoy (1941) gave aminophylline or placebos to sixty-eight patients over a period of two years, he said that the drug benefited about 75 per cent of the patients,

However, there is a reverse

of Evans and Hoyle

ed States, there was

failure to adduce any proof that these drugs are actually of value in coronary disease. In the latter studies, 209 courses of treatment with xanthines in

xanthines in the treatment of coronary disease far from satisfactory , but Gilbert (1944) still highly recommended them So the matter remains controversial!

Papaverine.—In 1942, Elek and Katz reported the highly successful employment of papaverine hydrochloride in about three-fourths of seventeen intensively studied patients with the anginal syndrome. Gray *et al.* (1945), giving doses of 1/2, 1½ and 3 grains (30, 100 and 200 mg.) four times daily for one week to ten ambulatory patients, found that the drug did not increase exercise ability and did not appear to be of practical value in the treatment of angina pectoris On the other hand, Swanson (1945) reported

as quinidine and that it has the advantage over the latter of not being a depressant of the heart but a powerful coronary dilator. Many men use the drug in higher dosage than that employed in the above-mentioned studies. According to N N.R. (1947), single doses of even 15 grains (1.0 gm.) are said to be nontoxic.

Sedatives and Codeine.—Many of these patients profit at times from the

about ten days reduced the dose as much as possible Riseman (1943) also reported that codeine was helpful in some of his patients

Nicotinic Acid (Niacin).—Neuwahl (1942) reported the administration of 100 to 200 mg of this agent by intravenous infusion in six cases, in most instances giving six infusions during a period of about three weeks There was said to have been subjective and objective evidence of improvement in

improve coronary blood flow, but this result was obtained only from dosage large enough to produce peripheral flushing, which in itself is an uncertain and unpleasant effect.

Sex Hormones.—There have been a number of favorable reports of the use of sex hormones in the anginal syndrome since the first report of Edwards *et al.* in 1939. The most favorable report is perhaps that of Lesser (1943) who used testosterone propionate in 25 mg doses for a total of five to twenty-five injections, with an average of eleven injections, the number of patients so treated being forty-one men and five women. It was said that in each of these cases subjective improvement was reported and that in four of the patients exercise tolerance tests substantiated the report No deleterious results were noted. In

also reported that testosterone therapy was helpful in seven of ten patients. However, Levine and Likoff (1943) carefully studied the use of this agent in eighteen patients treated for four weeks and one patient for seven weeks, and they felt that, considering the spontaneous variation in the clinical course of angina pectoris, they were unable to conclude that testosterone had been

[illegible]

as individuals having angina pectoris in association with the "male climacterium." It seems to me that surely we should strive to make haste slowly here.

Iodides.—Riseman (1943) reported that 12 per cent of a group of patients who were unresponsive to most other measures were helped by potassium iodide in 15 grain (1.0 gm) enteric-coated tablets given three or four times daily.

Cobra Venom.—Substantiating earlier favorable reports of one of themselves and of Parsonnet and Bernstein (1940), Freedberg and Riseman (1945) found cobra venom of value in seven of the twelve patients in which it was tried, there being an increase in the standardized exercise tolerance as well as clinical improvement, these good results having been said to occur in four of five patients who were unresponsive to the usual medication employed in angina. The optimum method of administration was 10 mouse units (1 cc.) three times a day the first day, followed by one injection daily for seven days; bi-weekly injections of 1 cc. were then necessary to maintain the effect. It was said that if escape from the drug occurred, repetition of the initial course of therapy sometimes produced beneficial effects. Local pain invariably occurred but was not severe enough to warrant discontinuance of treatment; no other [illegible]

Thiouracil.—The trouble with total thyroidectomy, and the reason for its practically complete abandonment, is that the initial risk is high and the subsequent complications, including myxedema, rather serious. However, it was quite a natural thing that with the introduction of the thiouracil group of drugs they should be tried out as a substitute for the operation; I believe that Raab (1945), and Ben-Asher (1945), independently made the first reports. Ben-Asher (1947), again reporting, said that he had found thiouracil to be beneficial in twenty-five of thirty-seven patients. Reveno (1946) also found the drug of some value in a smaller series of patients. Of course the usual toxic effects of thiouracil were noted in some of these patients, but now that propylthiouracil with its much lower toxicity is available we shall doubtless soon have a study of this type of therapy on a large series of patients.

Khellin.—An extract of the seeds of a plant growing wild in the eastern Mediterranean regions has been used in Egypt for the preparation of a compound known as khellin, with which Anrep *et al.* (1947) of the Faculty of Medicine of the University of Cairo, Egypt, said that they had effected excellent relief in over 150 cases of angina, using single or repeated doses of 1½ grain (100 mg) intramuscularly or the same or half the dosage by mouth three times daily. It may easily be that nothing will come of this, but then again [illegible] further

[illegible] availing themselves of the fact that referred pain from viscera can be abolished by procaine infiltration of tender areas in the somatic reference zone, found that

local block by procaine infiltration or ethyl chloride spray of somatic trigger areas located chiefly along the sternal borders afforded complete and prolonged relief of pain in nine patients with effort angina and acute myocardial infarction. They felt that because of their simplicity and effectiveness these procedures deserved extensive clinical trial.

CORONARY INSUFFICIENCY AND OCCLUSION

Disease of the coronary arteries has probably become the most common cause of mortality in this country with the exception of cancer. However, the correlation of bedside and pathologic findings in coronary occlusion, with the resultant recognition of it as a definite clinical entity, has taken place only in the twentieth century, in our own country largely as a result of the pioneer work of Herrick The interested reader is referred to the fine studies of Blumgart *et al* (1940) on the relationship of the clinical and pathologic findings in coronary disease, which it does not seem within my province to review here save to say that in general it seems conclusive that death occurs whenever a sufficiently large area of the myocardium undergoes ischemia, with or without necrosis, or when, because of ischemia, asystole, ventricular fibrillation, or congestive failure occurs. Some students in this field, notably Master (1947), would confine the term "coronary occlusion" to sudden complete closure as a sequel of progressive arteriosclerosis This type of attack is not related to effort and excitement and may take place during sleep or rest and while the individual is engaged in his routine activities. The infarct in these cases is usually large and the illness is prolonged and usually results in permanent changes in the heart. In "acute coronary insufficiency without acute occlusion" the episode is, according to Master, often related to exertion, excitement and emotion, and may occur after sexual intercourse, straining at stool, or following gastro-enteritis, or may be precipitated by tachycardia, auricular fibrillation, auricular flutter, shock, heart failure, hypoglycemia, operation, anesthesia, anoxemia of any type, carbon monoxide poisoning, acute hemorrhage, chronic anemia, hyperthyroidism, hypothyroidism, exposure to extremes of heat or cold, etc. In a severe episode of coronary insufficiency the heart muscle may contain many focal disseminated areas of subendocardial necrosis It seems that the incidence of acute coronary insufficiency is of the same magnitude and significance as that of acute coronary occlusion and that, in fact, in cases of acute sudden unexpected death acute coronary insufficiency is observed more frequently than is acute complete occlusion.

The victims of coronary disease are usually past fifty years of age, at least half of the men and practically all of the smaller number of women are said

having been found the basis of the occlusion in all cases. Similar though smaller series were also reported by Newman (1946) and Poe (1947); indeed, isolated case reports, and Stryker's (1946) review, show that coronary occlusive disease may occur even in infants and children. There is increasing evidence that the incidence of attacks is greatest in winter.

Unless death is sudden, the chief features of an acute coronary seizure are as follows: (a) *severe substernal or upper abdominal anginoid* pain, sudden in onset but of long duration (though according to Steincrohn, 1940, there is a characteristic rhythmicity and periodicity of the pain during the attack); (b) pinched, ashen gray or very pale facies often associated with a feeling of *impending death, but usually without the fixation in position so characteristic* of angina pectoris; (c) cold sweat and cold extremities; (d) the presence of large amounts of flatus; (e) acute emphysematous distention of the lungs with dyspnea or orthopnea and moist crackling râles at the lung bases, together with the onset of acute heart failure; (f) an early thready pulse with almost any form of arrhythmia, (g) rapid and often prolonged reduction in systolic pressure; (h) a diffuse, scarcely palpable cardiac impulse; (i) distant heart sounds and often a gallop rhythm; (j) a localized, evanescent pericardial friction rub; (k) short, mild fever with leukocytosis and a rapid sedimenta- [illegible] with a thorough [illegible] n [illegible] d coronary artery disease. *Coronary occlusion is often associated with or is the* cause of abdominal signs and symptoms, and occasionally it will closely simulate an acute surgical condition of the abdomen. Also in instances in which there are not [illegible] the coronary origin of the symptoms may [illegible] n with the patient's "indigestion"; but [illegible] n give an inkling of what is happening. Master *et al.* (1941) found that in nearly half of their 260 patients premonitory symptoms had been experienced: fatigue, weakness, gastric distress, dyspnea, palpitation, nervousness, dizziness, angina. Occasionally in whites, and frequently, according to Hunter (1946), in Negroes, occlusion may occur without any type of pain at all. The anoxemia test is considered by those qualified to perform and interpret it often helpful in diagnosis.

Katz and Mintz (1947) analyzed a series of 572 cases of recent myocardial infarction and drew the following conclusions with regard to prognosis: (a) hypertension appears to have no influence on the immediate prognosis; (b) diabetes definitely adds to the gravity of the situation especially in the female, (c) the persistence of anginal pain after the attack makes the immediate prognosis more grave; (d) pulse pressures of 25 mm. of Hg or less, or a systolic blood pressure drop to 90 mm. of Hg (100 mm. in the hypertensive) for several days, are poor prognostic signs, and so also is the presence of shock, (e) cardiac arrhythmias make the immediate prognosis grave, the most serious being frequent ventricular premature systoles and intraventricular block, (f) thromboembolic phenomena occurring during the infarction have a grave prognostic significance. In an analysis of the data on 422 private and ward patients who had recovered from an attack of acute coronary occlusion, Master (1947) found that 53 per cent returned to work after recovery, 92 per cent of these doing so within one year. Actually one-half resumed their occupation within three months after discharge *from* [illegible]

[illegible] resumed work, 38 per cent of those who had a second attack, and [illegible]

of those who had a third attack. Master concluded that probably well over 60 per cent of the patients recovered sufficiently to take up their customary occupations again had they wished to do so.

THERAPY

Nursing Care.—When he is first seen the patient is usually in a state of nervous if not actual circulatory shock, and therefore it is best if at all feasible to put him to bed at once wherever the attack has caught him, perhaps even without removal of clothes, for it is of the utmost importance to obtain quickly the maximum physical and emotional quiet with the minimum expenditure of either emotional or physical energy The obtaining of competent nursing assistance and the relief of the suffering are affairs of first moment, removal to the hospital or to his own home of secondary importance Then the siege must begin, a campaign whose sole object is to keep the patient *lying down* in bed for at least six weeks, to keep him quiet and unagitated during that time, and to cajole and induce him to like it. In the beginning he must not be permitted to move even enough to feed himself, and the rest of course must include use of the bed pan, but it seems certainly difficult to think of this as a performance replete with repose, cannot someone invent something? As few people should be seen, and as few affairs attended to, as possible. The use of sedative drugs is not contraindicated. Gilbert (1944) uses small doses of phenobarbital almost routinely as a sedative throughout the period of bed rest and frequently beyond it; he gives a dose of 1/2 grain (30 mg) at night and 1/4 grain (15 mg.) in the morning, just enough to decrease restlessness but not enough to cause drowsiness, and then if the patient is sleepless an additional barbiturate of the short-acting group, such as seconal or amytal, is employed at night to fetch sleep Two or three months of enforced invalidism is an ordeal few persons will accept without at least some show of stubborn resistance, but if the patient does not know with certainty that such a period lies before him there will likely be much less struggle Riesman admirably

condensing here the experience of many men in average cases; no time rules for these stages can be set, of course The indications that too much is being attempted are: sensation of choking, return of pain or pressure, cyanosis, shortness of breath on exertion, this patient must be returned to bed.

The above-described orthodox type of treatment of these cases by prolonged bed rest is predicated upon the following hypothetical advantages: (a) liability to cardiac rupture is lessened; (b) cerebral anoxia as a result of circulatory collapse is lessened, (c) such prolonged rest leads to the formation of a firmer and smaller scar. Recently, however, Harrison (1944) has shocked and surprised us into a reconsideration of the justification for a prolonged period of rest. He says that since most instances of rupture occur within the

first week or two, the theoretical advantage of maintaining the patient in the recumbent posture in order to counteract cerebral anoxia disappears after that time. Furthermore he questions whether a firmer and smaller scar is produced in a recumbent position since in his opinion cardiac work per beat is probably no greater and may be somewhat less in the sitting position than in the recumbent posture because the decline in blood pressure in the latter position is usually at least counterbalanced by the increased stroke volume in this posture Theoretical disadvantages of the prolonged rest in bed for these patients are listed by Harrison as follows: (a) recumbency invites edema of

may be brought about as a result of insistence on excessive caution during a period of many months. Harrison would not have recumbency prescribed following myocardial infarction for a longer period than two to three weeks after the more acute and alarming symptoms have subsided, nor would he force it it upon patients who are more comfortable sitting, and he would get elderly patients out of bed sooner than younger ones. Dock (1944) said that if the patient is afebrile and enjoys sitting up he sees no reason why he should not do so, and further that in men over fifty he knows that there are more complica-

cardiographic changes, though it is recognized that in some instances these changes may occur without actual necrosis of heart muscle.

Emergency Measures.—*Analgesics.*—It is practically always necessary to give morphine, ¼ to ½ grain (15 to 30 mg.), or dilaudid, 1/48 to 1/24 grain (1.25 to 2 5 mg.), at once. Larger doses are required to control this than any other pain—perhaps 1 grain of morphine in the first twelve hours; sometimes it is necessary to give it by vein. However, there are many careful clinicians who feel it is often best not to try to give enough morphine to conquer the pain *completely* in all cases. Scopolamine hydrobromide (hyoscine hydrobromide) may be safely used in addition to one of the opiate injections, in dose of 1/300 to 1/100 grain (0.2 to 0.6 mg.), but it is perhaps best not repeated under several hours. When pain persists for several days, attempt is usually made to change to codeine in doses of ¼ to ½ grain (15 to 30 mg.) every four hours. In morphine-resistant cases I have heard of pentothal being employed; but I should think one would have to proceed extremely cautiously with this agent. Lilienthal (1943) thought favorably of the application of leeches to the precordium; do old-fashioned barber shops still keep a stable of these animals?

Vasodilators.—It certainly seems to me that in the acute attack with cir-

their data, accumulated from studies in both animals and man, showed that xanthines have no effect in prolonging the clotting time of the blood, and that aminophylline solution, 10 to 20 cc., may be valuable if injected very slowly

Gilbert (1944) felt that it should be routinely employed in all cases until the pulse and respirations are approximately normal and cyanosis is improved. Boland (1940) made the important point that in his experience such concentrations as are ordinarily reached in a tent do not suffice for complete relief but that this end is achieved by the employment of an inhalation apparatus of one of the newer types that will deliver the 80 to 100 per cent concentrations he felt to be necessary.

Intravenous Infusion or Transfusion.—Gilbert (1944) expressed himself as opposed to the employment of intravenous dextrose and saline, or of plasma or blood transfusion, for the reason that such things may increase the blood volume and thus the load on the heart when it is delivering a decreased volume of flow through the kidneys.

Diet.—For the first two or three days the patient is very unlikely to desire much food. Sipping of cold charged water or swallowing small bits of ice will usually control nausea, the addition of bismuth subcarbonate and sodium

800 Calorie Diet (Master, Jaffe and Dack, 1936)

Breakfast	*Sample Menu*
100 gm. 12 per cent fruit	½ medium orange
10 gm cereal	2 tablespoons cooked cereal
200 cc skimmed milk	1 cup
1 egg	1 egg
15 gm bread	½ slice
Dinner	
60 gm meat	2 ounces meat
100 gm 3 per cent vegetable	½ cup spinach
100 gm. 12 per cent fruit	3 plums
15 gm. bread	½ slice
200 cc. skimmed milk	1 cup
Supper	
1 egg	1 egg
100 gm 3 per cent vegetable	¼ cup canned string beans
100 gm 12 per cent fruit	1 medium peach
15 gm bread	½ slice
200 cc. skimmed milk	1 cup

bicarbonate, each in 15-grain (1 gm) doses, will almost certainly do so; unfortunately, however, the nausea and possibly vomiting induced by morphine are not easily controlled by any means that I know—the employment of benze-

first week or two, the theoretical advantage of maintaining the patient in the recumbent posture in order to counteract cerebral anoxia disappears after that time. Furthermore he questions whether a firmer and smaller scar is produced in a recumbent position since in his opinion cardiac work per beat is probably no greater and may be somewhat less in the sitting position than in the recumbent posture because the decline in blood pressure in the latter position is usually at least counterbalanced by the increased stroke volume in this posture. Theoretical disadvantages of the prolonged rest in bed for these patients are listed by Harrison as follows: (a) recumbency invites edema of the lungs if there is a tendency toward the development of congestive heart failure; (b) both pulmonary infarction and a second myocardial infarction may be the result of rigid restriction of activity with consequent reduction in blood flow; (c) hypostatic pneumonia is especially likely to occur in elderly patients who remain in bed over a long period of time; (d) years of psychic invalidism may be brought about as a result of insistence on excessive caution during a period of many months. Harrison would not have recumbency prescribed following myocardial infarction for a longer period than two to three weeks after the more acute and alarming symptoms have subsided, nor would he force it it upon patients who are more comfortable sitting, and he would get elderly patients out of bed sooner than younger ones. Dock (1944) said that if the patient is afebrile and enjoys sitting up he sees no reason why he should not do so, and further that in men over fifty he knows that there are more complications due to absolute bed rest than can possibly be ascribed to exercise even

has yielded negative results during two weeks, the patient may be permitted restricted activity out of bed. Their collateral evidences of myocardial infarction are the following: (a) fever, (b) leukocytosis, (c) increased sedimentation rate, (d) increase of urobilinogen in the urine, and (e) of course serial electrocardiographic changes, though it is recognized that in some instances these changes may occur without actual necrosis of heart muscle.

Emergency Measures.—*Analgesics.*—It is practically always necessary to give morphine, ¼ to ½ grain (15 to 30 mg.), or dilaudid, 1/48 to 1/24 grain (1.25 to 2.5 mg.), at once. Larger doses are required to control this than any other pain—perhaps 1 grain of morphine in the first twelve hours, sometimes it is necessary to give it by vein. However, there are many careful clinicians who feel it is often best not to try to give enough morphine to conquer the pain *completely* in all cases. Scopolamine hydrobromide (hyoscine hydrobromide) may be safely used in addition to one of the opiate injections, in dose of 1/300 to 1/100 grain (0.2 to 0.6 mg.), but it is perhaps best not repeated under several hours. When pain persists for several days, attempt is usually made to change to codeine in doses of ¼ to ½ grain (15 to 30 mg.) every four hours. In morphine-resistant cases I have heard of pentothal being employed; but I should think one would have to proceed extremely cautiously with this agent. Lilienthal (1943) thought favorably of the application of leeches to the precordium; do old-fashioned barber shops still keep a stable of these animals?

maintain that if these drugs are used with proper precaution they will effect

their data, accumulated from studies in both animals and man, showed that xanthines have no effect in prolonging the clotting time of the blood, and that aminophylline solution, 10 to 20 cc., may be valuable if injected very slowly intravenously. He also advocated the intravenous injection of 1 grain (60 mg.) of papaverine hydrochloride, using a somewhat larger dose if the drug is given hypodermically. Falk (1942), and Gray *et al.* (1945), also spoke well of the

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bicarbonate, each in 15-grain (1 gm.) doses, will almost certainly do so; unfortunately, however, the nausea and possibly vomiting induced by morphine are not easily controlled by any means that I know—the employment of benze-

first week or two, the theoretical advantage of maintaining the patient in the recumbent posture in order to counteract cerebral anoxia disappears after that time. Furthermore he questions whether a firmer and smaller scar is produced in a recumbent position since in his opinion cardiac work per beat is probably no greater and may be somewhat less in the sitting position than in the recumbent posture because the decline in blood pressure in the latter

the lungs if there is a tendency toward the development of congestive heart failure; (b) both pulmonary infarction and a second myocardial infarction may be the result of rigid restriction of activity with consequent reduction in blood flow; (c) hypostatic pneumonia is especially likely to occur in elderly patients who remain in bed over a long period of time; (d) years of psychic invalidism may be brought about as a result of insistence on excessive caution during a period of many months. Harrison would not have recumbency prescribed following myocardial infarction for a longer period than two to three weeks after the more acute and alarming symptoms have subsided, nor would he force it it upon patients who are more comfortable sitting, and he would get elderly patients out of bed sooner than younger ones. Dock (1944) said that if the patient is afebrile and enjoys sitting up he sees no reason why he should not do so, and further that in men over fifty he knows that there are more complications due to absolute bed rest than can possibly be ascribed to exercise even in those patients who never go to bed or who go back to work as soon as the initial bout of pain and fever has subsided. Aagaard and Watson (1945) have been willing to say that when daily search for collateral evidence of infarction

cardiographic changes, though it is recognized that in some instances these changes may occur without actual necrosis of heart muscle.

Emergency Measures.—*Analgesics.*—It is practically always necessary to give morphine, $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg.), or dilaudid, 1/48 to 1/24 grain (1.25 to 2 5 mg.), at once. Larger doses are required to control this than any other pain—perhaps 1 grain of morphine in the first twelve hours; sometimes it is necessary to give it by vein. However, there are many careful clinicians who feel it is often best not to try to give enough morphine to conquer the pain *completely* in all cases. Scopolamine hydrobromide (hyoscine hydrobromide) may be safely used in addition to one of the opiate injections, in dose of 1/300 to 1/100 grain (0 2 to 0.6 mg.), but it is perhaps best not repeated under several hours When pain persists for several days, attempt is usually made to change to codeine in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg.) every four hours. In morphine-resistant cases I have heard of pentothal being employed; but I should think one would have to proceed extremely cautiously with this agent. Lilienthal (1943) thought favorably of the application of leeches to the precordium; do old-fashioned barber shops still keep a stable of these animals?

Vasodilators.—It certainly seems to me that in the acute attack with circulatory collapse and a low blood pressure the use of agents of this group is at least theoretically extremely inadvisable; however, there are a few men who maintain that if these drugs are used with proper precaution they will effect

great relief. Gilbert (1944) said he gives atropine sulfate, 1/100 to 1/75 grain (0.6 to 0.8 mg.), hypodermically routinely in all cases where the occlusion is at all recent, the theory being that reflex vasoconstriction of the arteries in the uninvolved heart muscle is thus counteracted. Gilbert *et al.* (1947) felt that their data, accumulated from studies in both animals and man, showed that xanthines have no effect in prolonging the clotting time of the blood, and that aminophylline solution, 10 to 20 cc., may be valuable if injected very slowly

Gilbert (1944) felt that it should be routinely employed in all cases until the pulse and respirations are approximately normal and cyanosis is improved. Boland (1940) made the important point that in his experience such concentrations as are ordinarily reached in a tent do not suffice for complete relief but that this end is achieved by the employment of an inhalation apparatus of one of the newer types that will deliver the 80 to 100 per cent concentrations he felt to be necessary.

Intravenous Infusion or Transfusion.—Gilbert (1944) expressed himself as opposed to the employment of intravenous dextrose and saline, or of plasma or blood transfusion, for the reason that such things may increase the blood volume and thus the load on the heart when it is delivering a decreased volume of flow through the kidneys.

Diet.—For the first two or three days the patient is very unlikely to desire much food. Sipping of cold charged water or swallowing small bits of ice will usually control nausea; the addition of bismuth subcarbonate and sodium

800 Calorie Diet (Master, Jaffe and Dack, 1936)

Breakfast	*Sample Menu*
100 gm. 12 per cent fruit	½ medium orange
10 gm. cereal	2 tablespoons cooked cereal
200 cc skimmed milk	1 cup
1 egg	1 egg
15 gm bread	½ slice
Dinner	
60 gm meat	2 ounces meat
100 gm 3 per cent vegetable	½ cup spinach
100 gm 12 per cent fruit	3 plums
15 gm bread	½ slice
200 cc. skimmed milk	1 cup
Supper	
1 egg	1 egg
100 gm 3 per cent vegetable	¾ cup canned string beans
100 gm 12 per cent fruit	1 medium peach
15 gm bread	½ slice
200 cc. skimmed milk	1 cup

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Emergency Measures.—*Analgesics.*—It is practically always necessary to give morphine, ¼ to ½ grain (15 to 30 mg.), or dilaudid, 1/48 to 1/24 grain (1.25 to 2.5 mg.), at once. Larger doses are required to control this than any other pain—perhaps 1 grain of morphine in the first twelve hours; sometimes it is necessary to give it by vein However, there are many careful clinicians who feel it is often best not to try to give enough morphine to conquer the pain *completely* in all cases. Scopolamine hydrobromide (hyoscine hydrobromide) may be safely used in addition to one of the opiate injections, in dose of 1/300 to 1/100 grain (0.2 to 0.6 mg.), but it is perhaps best not repeated under several hours. When pain persists for several days, attempt is usually made to change to codeine in doses of ¼ to ½ grain (15 to 30 mg.) every *four* hours In morphine-resistant cases I have heard of pentothal being employed; but I should think one would have to proceed extremely cautiously with this agent. Lilienthal (1943) thought favorably of the application of leeches to the precordium; do old-fashioned barber shops still keep a stable of these animals?

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intravenous emergency employment of papaverine.

Oxygen.—In recent years Barach and Levy have been advocating the use of oxygen in cases of coronary thrombosis (for methods see Pneumonia). Many men testify to its ability to relieve dyspnea, cyanosis, restlessness and pain—Gilbert (1944) felt that it should be routinely employed in all cases until the pulse and respirations are approximately normal and cyanosis is improved. Boland (1940) made the important point that in his experience such concentrations as are ordinarily reached in a tent do not suffice for complete relief but that this end is achieved by the employment of an inhalation apparatus of one of the newer types that will deliver the 80 to 100 per cent concentrations he felt to be necessary.

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Diet.—For the first two or three days the patient is very unlikely to desire much food. *Sipping of cold charged water or swallowing small bits of ice will* usually control nausea; the addition of bismuth subcarbonate and sodium

800 CALORIE DIET (MASTER, JAFFE AND DACK, 1936)

Breakfast	*Sample Menu*
100 gm 12 per cent fruit	½ medium orange
10 gm cereal	2 tablespoons cooked cereal
200 cc skimmed milk	1 cup
1 egg	1 egg
15 gm bread	½ slice
Dinner	
60 gm meat	2 ounces meat
100 gm 3 per cent vegetable	½ cup spinach
100 gm 12 per cent fruit	3 plums
15 gm bread	½ slice
200 cc. skimmed milk	1 cup
Supper	
1 egg	1 egg
100 gm 3 per cent vegetable	¾ cup canned string beans
100 gm 12 per cent fruit	1 medium peach
15 gm bread	½ slice
200 cc skimmed milk	1 cup

bicarbonate, each in 15-grain (1 gm.) doses, will almost certainly do so; unfortunately, however, the nausea and possibly vomiting induced by morphine are not easily controlled by any means that I know—the employment of benze-

drine sulfate (*amphetamine*) *for this* purpose, *successfully* reported by Guyot (1941), seems to me a very radical procedure; indeed, I believe the consensus to be that benzedrine is contraindicated at least during the acute stages of coronary disease. Dry toast, chicken, buttermilk, apple sauce, strained vegetables, tea or coffee may all be added gradually and in small quantities. T

three and preferably four weeks they limit fluids to *1000* or *1200* cc. and calories to 800; on page 761 is a sample diet containing 100 gm. carbohydrates, 50 gm. proteins, 20 gm. fat, with adequate vitamins and calcium. They claim as much reduction in basal metabolic rate with this regimen as is accomplished by thyroidectomy and that patients feel so well under it that persuasion is often required to get them to increase their food intake.

Gilbert (1944) said he sees no reason why the moderate use of coffee and alcohol should not be permitted but that tobacco should be omitted unless *to do so causes actual restlessness,* and even then *its* use *should be limited* as much as possible.

Care of the Bowels.—Straining had best be avoided by the use of liquid petrolatum. It is best to permit the costiveness induced by the opiates in ... the patient

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Digitalis.—I think that upon the whole the profession is fearful of the use *of digitalis in coronary occlusion in the belief that it may:* (a) *rupture* the infarct through increasing the forc ...

the heart to ventricular tachycard

such an authority as Gold (1939),

is certain that there are no grounds for any of these fears. He feels that the indications for digitalis in coronary occlusion are precisely those that would obtain otherwise, *i.e*, the drug should be used if there supervenes an auricular fibrillation or a right or left ventricular failure. Such disturbances occur very rarely during the early days of a coronary episode and not always by any means at a later period or during the subsequent attacks; therefore

in agreement with the position of Gold, felt that unless ... abundant clinical experience seems to justify

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mortality higher in those patients who received the drug, but in Katz' discussion of the paper he said that of course he uses digitalis if the patient shows *progressive* congestive failure

Quinidine.—Ventricular tachycardia being an arrhythmia much feared after coronary occlusion, there has arisen some interest, probably initiated by Levine (1936), in the *"prophylactic" use of quinidine* to prevent this occurrence; ventricular tachycardia going over into fibrillation of course

means death. Borg (1939), employing quinidine sulfate 3 grains (0.2 gm) three times daily in a large group of clinic patients of the sort in whom sudden death was to be expected, felt that the drug probably lessened the incidence of such deaths. Woods and Barnes (1941), at the Mayo Clinic, seemed convinced that it is rational and probably important to give the drug to any patient who has had an occlusion, particularly if the patient is experiencing frequent premature ventricular contractions, and in 1947, Barnes kindly expressed himself to me as still of this opinion Dietrick (1945) said also that though he does not subscribe to the prophylactic use of the drug he does not hesitate to use it if premature ventricular contractions, or ventricular tachycardia itself, appears. Gold (1947) does not believe that the use of quinidine as a routine prophylactic agent is practical, for if the dose is fairly large it is dangerous and if it is small it will fail to prevent the disorders of rhythm in the majority of cases He feels that the incidence of arrhythmias in coronary thrombosis is very small and that with appropriate doses of quinidine the attack of rhythm disorder can be promptly controlled when it occurs. Gilbert (1944), however, said that he had seen untoward effects from the use of quinidine and that therefore he does not employ it.

Dicumarol and Heparin.—In his preliminary report of a study of the use of dicumarol in coronary thrombosis in the Vascular Clinic at New York Postgraduate Medical School of Columbia University, Wright (1946) said that it is premature to make extensive claims about the merits of dicumarol in this situation because adequate controls with which to determine its value statistically will not be available, and will be of little value, unless several subdivisions depending on the severity, extension and complications of each group are studied separately. Each of these subdivisions, in his opinion, must contain a statistically significant number of controls and treated patients, an evaluation of this sort has been planned as a cooperative venture in a group of hospitals under the auspices of the American Heart Association and will be awaited with much interest Of course it must be obvious to anyone that the task of evaluating the effectiveness of an agent in preventing further thromboses in a particular patient is obliged to be difficult because we have no means at present of predicting with certainty which patient will experience a rapid series of secondary episodes of thrombosis, which one will have one or more embolic phenomena, or which one will experience an uneventful recovery from the immediate attack. However, in Wright's series of seventy-six patients treated with dicumarol, the findings suggested to him that the drug may be of value as a preventive measure against propagation, multiple serial attacks of coronary thrombosis within short spaces of time, mural and thebesian vein thromboses, and embolic phenomena. He felt it impossible to state from his study to what degree the use of the agent will affect the longevity of the patient. There was no evidence in this study that, once dicumarol's use has been discontinued and the blood prothrombin level has returned to normal, any effect is exerted which decreases the risk of further attacks of coronary thrombosis in the same individual. Likewise there was no evidence adduced that dicumarol aggravated or complicated the course of the patient with coronary thrombosis.

Since Wright's paper was published several favorable reports of the use of dicumarol have appeared. Peters *et al.* (1946), of the University of Maryland Medical School, compared fifty dicumarolized with sixty non-dicumarolized patients and found that the incidence of clinical embolism was 16 per cent

known as phlegmasia alba dolens. To the rule that the clot is firmly attached to the walls of the vein, Ochsner (1946) pointed out two exceptions: first, the possible formation of a proximal coagulation thrombus that may become detached and produce a very small pulmonary infarction; and second, the production of septic emboli when *fragments break off of the fixed clot that is* being liquefied by liberated proteolytic enzymes in suppurative thrombosis, usually seen only in patients with severe pelvic infections, often as the result of criminal abortion.

In phlebothrombosis the process begins with a thrombus that arises in the plantar or calf muscle veins and extends from there into the deep veins of the thighs and pelvis. This thrombus, anchored only at its lower end, is a freely-waving eel-like formation that continues to grow upward in the direction of the blood stream. Parts of it may, and frequently do, break off and cause massive pulmonary embolism. Bauer (1946) feels that in the majority of instances of phlebothrombosis the thrombus eventually becomes attached to the vessel wall along its entire length, the vessel then becoming the seat of an inflammatory process, and what began as phlebothrombosis ends as thrombophlebitis and phlegmasia alba dolens. However, Ochsner (1946) is of the opinion that the ultimate firm attachment of the thrombus in phlebothrombosis is a late and infrequent phenomenon and should not be anticipated. The cause of phlebothrombosis is not known, but it is not ... lower extremities ... that the circula- ... iteal veins if the ...

... of many observers that some alterations in the blood's constituents account for the formation of the clot, though undoubtedly the precipitating factor is circulatory stasis, Ochsner (1946) expressed himself as feeling that excessive ... the phlebothrom- ... presence ... the foot ... y be no elevation in the temperature or pulse rates and in the beginning no edema of the foot or leg. Oftentimes in these cases a sudden sharp pain in the chest, signalling the occurrence of embolism, will be the first sign that a phlebothrom- ... men to compress the calves ... he Homans maneuver—the ... detect phlebothrombosis in ... these maneuvers. ...

nemius muscle against the posterior surface ... other. Moses (1946) remarked that one calf may be slightly ... has routinized examin... the calf and sa... compression from

side to side in the palm of the hand elicits markedly less evidence of tenderness than deep exploring pressure with the finger-tips, presumptive diagnosis of phlebothrombosis is indicated, and that if peripheral neuritis is then ruled out by determination that cutaneous sensation, position sense, vibratory sense and the deep reflexes are normal, the final diagnosis of phlebothrombosis is warranted. Phlebography, so stoutly championed by Bauer (1946) in Sweden, is not practiced in this country nearly so extensively as it formerly was. Homans (1947) said it could not be too strongly emphasized in his opinion that the more silent and insidious the deep thrombosis the more dangerous it is, and that when one leg is tensely swollen and the other seemingly normal, embolism is threatened less by the swollen limb than by the apparently innocent one.

Small pulmonary emboli may only produce substernal pain, faintness, coughing or bloody sputum, but a massive embolus may result in sudden death. In these latter cases the signs of complete circulatory dissolution are due not only to sudden obstruction of the pulmonary arterial tree but also to intense vasospasm of the unaffected part of the pulmonary artery, to sudden coronary insufficiency, and to bronchial spasm In a non-fatal pulmonary embolism the symptoms of precordial pain, dyspnea, cyanosis and other features similar to those of myocardial infarction may make differential diagnosis difficult However, diminished voice and breath sounds and moist râles are frequently heard over the involved portion of the lung, pleural friction sounds are often heard, and there may be hemoptysis Allen *et al.* (1948) found it a point of considerable differential diagnostic value that in the vast majority of instances the lower lobes of the lungs are involved more frequently than the upper It is said that there are certain electrocardio-
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simulated pneumonia, angina pectoris, acute myocardial infarction, pleurisy, vascular collapse or acute heart failure in a large percentage of instances

PREVENTIVE MEASURES

Preoperative Precautions.—Ochsner (1946) believes it important that patients with cardiovascular disease be treated to reestablish circulatory function before a contemplated operative procedure is undertaken, and that, as stressed by Duryee (1944), the patient should refrain from smoking for a period of ten to fourteen days preoperatively Furthermore, in order to

infection, neoplastic disease or trauma Of course the correction of anemia or polycythemia before operation is extremely desirable, and since obesity predisposes to venous thrombosis, reduction in weight before elective surgical procedures is of importance, though usually difficult to achieve

Exercise and Ambulation.—It is of interest that Dock stated in a Cornell Therapeutic Conference, in 1944, that in his opinion absolute bed rest kills more patients than anesthesia and all the drugs in the pharmacopoeia added

together. *Nowadays*, in addition to the avoidance of tight dressings and earnest attempts to avoid and combat abdominal distention, it is definitely the vogue to elevate the foot of the bed in order to assist the leg veins in *emptying, to enjoin* the patient to contract his muscles frequently and actively, particularly his calf muscles against a resistance, and to get him out of

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per cent. The patient should also be encouraged to breathe deeply and be instructed to *avoid chilling, which may produce vasospasm and influence* venous thrombosis. A definite point needs to be made regarding early ambulation, namely, that it should actually *be* ambulation. Both Ochsner (1947) and Allen *et al.* (1947) *have emphasized the fact that the patient should actually* get out of bed and walk and then lie down again and that he should not sit in a chair with his feet on the floor after having actually been lifted there from the bed by a well-meaning attendant. *It is actual muscular activity* to keep the leg veins empty that is the desirable end of early ambulation.

Femoral Vein Interruption and the Use of Anticoagulants.—This is a truly controversial subject at the present time. Perhaps the most extreme advocate

tions for the preventive use of anticoagulants is after abdominal hysterectomy, for 4 per cent of patients who undergo this operation have postoperative

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has been ambulatory for three to seven days Arthur W. Allen (1947), and his associates at the Massachusetts General Hospital, said it seemed to them that the age group between forty and sixty-five is the correct one in which to use dicumarol prophylactically; in their study the incidence of *thrombosis* and embolism was lowered to about 25 per cent of that seen in the control group in another ward who did not receive the drug. It was said that in no *case did severe hemorrhage occur that could not have been accounted* for otherwise and that there was no more bleeding into the tissues near the operative wound than is ordinarily seen in patients not receiving dicumarol. *This group* at the Massachusetts General Hospital believe, however, that in patients beyond the age of sixty-five, and in selected prematurely old or debilitated persons, the best method of protection is interruption of the superficial femoral veins. They stated that in only one instance in the 634 patients so treated had there been any evidence of subsequent thrombophlebitis or

and that only the slightest amount of transient swelling is observed

olby (1947), of the same hospital,

vein interruption as a prophylactic

procedure is being done with increasing frequency in selected patients. But Masson (1946), of the Mayo Clinic, said that in his experience it has been difficult to decide when and what vein should be *ligated and that he thought*

ligation of any veins above the common femoral must be considered a major procedure in an already sick patient. So, as I have said, the subject is controversial.

The details of heparin and dicumarol employment will be found in the section on their use in the treatment of phlebothrombosis (see below). Bancroft (1947) said that while he feels that no anticoagulant compares favorably with these two agents once thrombosis has occurred, he has had very good success over a considerable period of years in the use of sodium thiosulfate as a preventive measure. He gives 10 cc. of a 10 per cent solution intravenously for several days in succession in cases in which he has reason to suspect that phlebothrombosis might occur, and says that the drug is cheap, has apparently no toxic effect, is not particularly annoying to the patient, and has seemed in his experience to be fully protective

TREATMENT OF THROMBOPHLEBITIS

Procaine Block of the Sympathetic Ganglia.—The experimental and clinical work of Ochsner and DeBakey (1940), confirming earlier French studies, seems to have established vasospasm affecting both the arterial and venous systems as the most plausible theory to account for the edema in thrombophlebitis Procaine block of the regional sympathetic ganglia relieves the spasm and causes the symptoms quickly to subside. Ochsner (1946) said that in his experience relief of pain is complete and permanent in 90 per cent of the patients following a single block, a second block being necessary to give permanent relief in the other 10 per cent Sixty-five per cent of his patients were fever-free in forty-eight hours, 24 per cent in three to five days, and 7 per cent in six to eight days; edema subsided within four days or less in 56 per cent, in five to eight days in 32 per cent, in nine to ten days in 8 per cent, and in eleven to twelve days in 3 per cent Aycock and Hendrick (1947), and indeed many other observers, have had similar results Aycock and Hendrick inject 10 cc. of a 1 per cent solution of procaine hydrochloride into the first to fourth ganglia and 10 cc. of monobromosaligenin (bromsalizol) into each of the second and third ganglia. It is said that the action of the procaine is immediate but that its effects disappear within a number of hours, whereas the action of the monobromosaligenin, though coming on slower, lasts from five to ten days. In addition to blocking of the ganglia the limb is elevated until the edema disappears, and then active exercise is begun The patient is caused to wear an elastic stocking or bandage for some weeks if there is persistence of the edema after he is allowed out of bed, the bandage incorporating the foot and leg up to and above the knee.

Masson (1946), of the Mayo Clinic, said that blocking is an efficient and valuable method of causing vasodilatation with the relief of pain and reduction

with sympathetic block since to do so might predispose to retroperitoneal

together. Nowadays, in addition to the avoidance of tight dressings and earnest attempts to avoid and combat abdominal distention, it is definitely the vogue to elevate the foot of the bed in order to assist the leg veins in emptying, to enjoin the patient to contract his muscles frequently and actively, particularly his calf muscles against a resistance, and to get him out of bed as soon as possible Adams (1947), of the Lahey Clinic, said that since they had started the energetic postoperative use of foot exercises their incidence of thromboembolic phenomena had been reduced by about 50 per cent. The patient should also be encouraged to breathe deeply and be instructed to avoid chilling, which may produce vasospasm and influence venous thrombosis. A definite point needs to be made regarding early ambulation, namely, that it should actually *be* ambulation. Both Ochsner (1947) and Allen *et al.* (1947) have emphasized the fact that the patient should actually get out of bed and walk and then lie down again and that he should not sit in a chair with his feet on the floor after having actually been lifted there from the bed by a well-meaning attendant. It is actual muscular activity to keep the leg veins empty that is the desirable end of early ambulation.

Femoral Vein Interruption and the Use of Anticoagulants.—This is a truly controversial subject at the present time. Perhaps the most extreme advocate of surgery as the method of choice is Ochsner (1946), who says he feels that

extensive studies at the Mayo Clinic had indicated to them that dicumarol is effective in preventing thrombosis or in preventing its extension once it has occurred; he said experience had taught them that one of the certain indications for the preventive use of anticoagulants is after abdominal hysterectomy, for 4 per cent of patients who undergo this operation have postoperative venous thrombosis or embolism and 0 7 per cent die of fatal embolism. Allen said that at the Clinic they ordinarily begin the use of dicumarol on the second or third postoperative day and continue its administration until the patient has been ambulatory for three to seven days. Arthur W. Allen (1947), and his associates at the Massachusetts General Hospital, said it seemed to them that the age group between forty and sixty-five is the correct one in which to use dicumarol prophylactically; in their study the incidence of thrombosis and embolism was lowered to about 25 per cent of that seen in the control group in another ward who did not receive the drug. It was said that in no case did severe hemorrhage occur that could not have been accounted for otherwise and that there was no more bleeding into the tissues near the operative wound than is ordinarily seen in patients not receiving dicumarol. This group at the Massachusetts General Hospital believe, however, that in patients beyond the age of sixty-five, and in selected prematurely old or debilitated persons, the best method of protection is interruption of the superficial femoral veins. They stated that in only one instance in the 634 patients so treated had there been any evidence of subsequent thrombophlebitis or embolism and that only the slightest amount of transient swelling is observed in the feet and ankles at a later period. Colby (1947), of the same hospital, said that in the Urological Service femoral vein interruption as a prophylatic procedure is being done with increasing frequency in selected patients. But Masson (1946), of the Mayo Clinic, said that in his experience it has been difficult to decide when and what vein should be ligated and that he thought

promiscuous ligation as a prophylactic measure was not warranted especially in view of the possible sequelae that might be a definite handicap to the pa-

versial.

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elastic stocking or bandage for some weeks if there is persistence of the edema after he is allowed out of bed, the bandage incorporating the foot and leg up to and above the knee.

Masson (1946), of the Mayo Clinic, said that blocking is an efficient and valuable method of causing vasodilatation with the relief of pain and reduction of lymphedema; in his opinion, however, much the same results can be obtained by properly applied heat and proper elevation in a sling with suspension above the bed; in addition, whiskey by mouth has some vasodilating effect in patients in good condition and tends to relieve tension and improve morale. It would certainly seem inadvisable to use anticoagulant agents concomitantly with sympathetic block since to do so might predispose to retroperitoneal

hemorrhage. Hendrick (1947) well emphasized that one should be careful not to do paravertebral blocks for phlebothrombosis but only for thrombophlebitis.

Caudal Anesthesia.—Several observers have reported good effects from the institution of continuous caudal anesthesia in cases of thrombophlebitis, but since, as pointed out by Benson (1946), the standardization of medication, dosage and duration of treatment are problems requiring further study before a settled routine of therapy is established, it does not seem to me advisable to attempt a description of the methods at this time.

Vein Ligation.—Allen *et al.* (1947) said that ligation of the vena cava is indicated if thrombophlebitis is the cause of repeated septic infarcts

TREATMENT OF PHLEBOTHROMBOSIS

Anticoagulants.—Loewe and Hirsch (1947) extolled the value of anticoagulant therapy not only to prevent the propagation of the clot but also to promote the dissolution of red cell clots that contain a minute amount of fibrin but are not as yet organized They also believe that such therapy maintains patent the adjacent collaterals and tributaries that ordinarily would become involved in the thrombotic occlusive process and feel one can assume that the same thing also occurs in obstructed lymphatic vessels. Allen (1947), of the Mayo Clinic, expressed the opinion that the expert use of anticoagulants produces results better than those following ligation of veins with the exception of instances in which venous thrombosis and pulmonary embolism occur repeatedly over a considerable period of time, ligation of the vein being the superior therapeutic measure in these cases because of the difficulty of administering anticoagulant therapy over a long period. Evans and Boller (1947) said that at the Lahey Clinic anticoagulant therapy had been the treatment of choice since early 1942 Homans (1946) expressed the feeling that should the anticoagulants prove fully as life-saving as operative measures—as many observers believe that they have—they should probably be preferred as securing a better post-phlebitic leg.

Allen (1947), of the Mayo Clinic, listed the following contraindications to the use of anticoagulants: (1) ascorbic acid and vitamin K deficiencies or hepatic disease, because anticoagulants may magnify the tendency to bleed,
... enhanced and
impairment
anticoagu-
ions on the
brain or spinal cord, because even a small amount of bleeding in these regions may ... lesions or open wounds, because of magnifica... ndications of Allen *et* ... re hyper-tension, dise... bleeding in operation, diabetes, arthritic patients taking salicylates. Bancroft (1947) said that there are three types of cases in which he would hesitate to use ... the termination of pregnancy; second, ... 'egia from hemorrhage; and third, in ... occlusion Hendrick (1947) said his group had found dicumarol to be contraindicated in prostatic surgery.

Dicumarol.—Allen (1947), in reporting the use of dicumarol in 1686 post-operative cases at the Mayo Clinic, stated that 300 mg. is given on the first

dicumarol only 100 mg may be given instead of 200 mg, and conversely if the blood is insensitive to the effect 300 mg may be given instead of 200 mg He said furthermore that if the percentage of prothrombin is decreasing rapidly but is more than 20, no dicumarol is given; if on the other hand the percentage is rising rapidly but has not yet reached 20 per cent, the drug is given on that day.

In this series of 1686 postoperative cases, minor hemorrhages (epistaxis, hematuria, petechiae and ecchymoses) occurred in 3.1 per cent; it was said that in such instances the intravenous administration of 30 to 60 mg. of menadione (vitamin K) in order to return the prothrombin value to somewhat less than 30 per cent will permit the cautious resumption of dicumarol therapy. If, however, as is rarely the case, the complications are serious it may be necessary to give enough vitamin K to return the values for prothrombin to normal, in these cases, if necessary, treatment with dicumarol may be resumed cautiously when bleeding has ceased. Major bleeding (usually from operative wounds) occurred in 1 9 per cent of the patients in this series, two patients died, but analysis of these two case reports makes it doubtful that either of these patients died as a result of dicumarol administration.

Allen said that if an emergency operation must be performed on a patient receiving dicumarol, transfusions and large amounts of vitamin K may be given to return the prothrombin values toward normal.

Heparin.—Loewe and Hirsch (1947) felt that the delayed action, the potential hazards and the requisite complicated but indispensable laboratory *procedures militate against dicumarol as the anticoagulant of choice.* The

said that in comparison with material treated in the old conservative way heparin treatment resulted in depressing the mortality to less than one-tenth and in reducing the time in bed from the previously customary forty days to about five days. He said also that there was reason to believe that heparin-treated patients would escape the troublesome after-effects of permanent swelling of the leg and later on brown induration and ulcers. Heparin was formerly given by continuous intravenous drip in a solution containing 100 to 200 mg. of heparin in 1000 cc. of 5 per cent dextrose, the flow rate being about 20 drops per minute. However, this was expensive and caused discomfort to the patient and a strain upon the attendant staff. Latterly it has *been found cheaper, less bothersome and just as effective to give 50 mg* intravenously at four-hour intervals. Loewe and Hirsch (1947) felt that the Pitkin menstruum, developed some years ago to retard the rate of release of water-soluble drugs injected subcutaneously or intramuscularly, is well suited for the introduction of heparin in these cases. They reported that the use of heparin in this form in 100 patients representative of all forms of venous thrombo-embolic disease had yielded results that were eminently satisfactory as judged by the effective control of pulmonary embolization, the prompt amelioration of pain and discomfort, the rapid recession of edema, the reduction in morbidity, the acceleration of convalescence, and the virtual

absence of residual edema, particularly when patients were treated without delay. They said that the span of treatment for uncomplicated thrombophlebitis or phlebothrombosis was ten days to two weeks, an additional week or two of therapy being required for patients who had experienced pulmonary embolization. Evans and Boller (1946), of the Lahey Clinic, said that for several years they have been employing heparin during the period of two to five days required for dicumarol to exert its effect. Latterly, the heparin-Pitkin preparation has been substituted for intravenous heparin and their experience has shown them that the following dosage is most effective: to patients under 150 pounds (68 kg.) they give a 1-cc. ampule of 100 mg. of heparin without vasoconstrictor agents added and a 1-cc. ampule containing 100 mg. of heparin with the addition of vasoconstrictors (the preparation is available commercially in the two forms). If the patient is over 150 pounds he is given 100 mg. of heparin-Pitkin without vasoconstrictor and 200 mg. with vasoconstrictor. A daily prothrombin percentage is determined to guide dicur

daily to guide heparin-

agulation time returns

thrombin time to at least 69 per cent. The initial dose of 200 mg. of dicumarol is given to a patient under 150 pounds, 300 mg. to a patient over 150 pounds A daily maintenance dose of 100 mg. of dicumarol is given whenever the prothrombin is over 65 per cent. Loewe and Hirsch (1947) used papaverine in addition to their heparin-Pitkin menstruum therapy, giving 1 to $1\frac{1}{2}$ grains (60 to 90 mg.) every four hours intramuscularly or intravenously, then later maintenance dosage by mouth. Bancroft (1947) said that while the pain caused by the heparin-Pitkin solution of Loewe is so great that the patient is likely to oppose the third injection, he nevertheless feels that this is a great advance and that he is certain this difficulty will be remedied; indeed, Loewe and Hirsch intimated that this had already been partially accomplished by careful buffering that has made the pH of the gel more physiologically acceptable.

Bauer (1946) expressed the consensus of those who use heparin in saying that it is of the utmost importance that the patient get up when or before the heparinization is terminated because when the agent is stopped he is totally

patient cannot get up he should be made to perform all the tension and relaxation exercises of the muscles that are practicable within a plaster cast and the

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takes precedence as far as urgency is concerned over any other case service except that of massive hemorrhage. In justification of his position, Ochsner says that while he is sure that the anticoagulants will prevent the for-

mation of new thrombi, he is also sure that they will not guarantee against the detachment of the thrombus that is already there Allen *et al.* (1947) stated that at the Massachusetts General Hospital they had given up the use of anticoagulant agents in the treatment of phlebothrombosis and early thrombophlebitis because in their hands the treatment was unsatisfactory, some patients doing well on heparin therapy but the process flaring up in them again shortly after heparinization was stopped, and one such patient succumbing to massive embolus during this treatment. They therefore concluded that it was illogical to use this method of treatment unless it was preceded by interruption of the femoral veins. This is also the opinion of Aycock and Hendrick (1947), of the University of Maryland Medical School, and numerous other surgical groups throughout the country. Some men merely ligate the vein above the thrombus and some in addition perform thrombectomy (opening of the vein and removal of the clot by suction until free bleeding occurs). Bancroft (1947) said that while he performs thrombectomy where it seems to be indicated, he does feel there is some slight danger that in removing the clot a piece may break off and extend upward into the vein. He also expressed himself in dis- [illegible]

[illegible]

TREATMENT OF PULMONARY EMBOLISM

De Takats and Fowler (1945) reiterated what the senior author had pointed out several years earlier, namely, that about 60 per cent of patients with fatal emboli live from one hour to several days, which means that in the majority of instances there is sufficient time to institute treatment for the episode itself. Certainly, n [illegible]
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studies De [illegible]
that a wide [illegible]
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lead to pulmonary edema in the presence of an increased pressure in the pulmonary arteries such as exists in cases of pulmonary embolism De Takats therefore gives 1/75 grain (0.8 mg.) of atropine sulfate hypodermically [illegible]

1 grain (60 mg.) of papaverine hydrochloride is also given intravenously. The atropine and papaverine administration is repeated three or four times a day. De Takats has continued to employ this atropine-papaverine measure with satisfaction for a number of years at his hospital.

Meigs and Ingersoll (1946) said that all the surgeons of the Massachusetts General Hospital are convinced that interruption of the femoral veins is essential after a sublethal embolus or infarct. De Takats (1947) said that when the origin of the embolism is recognizable he ligates above the level of the thrombus, which may be at the superficial femoral, the common iliac or the vena cava When the [illegible]

[illegible]

when one stops the administration of the anticoagulant drugs this must be done gradually.

THROMBOANGIITIS OBLITERANS

(Buerger's Disease)

This peculiar disease, first described by Buerger in 1908, is an inflammatory affection of the deep-seated arteries and veins and the superficial veins of the lower extremities, occasionally of the upper extremities. It occurs principally in males between the ages of twenty and fifty, though women, in whom it seems to be a milder affection, are also very occasionally afflicted. We nowadays do not look upon this as almost exclusively a malady of Jews; of Horton's (1938) 927 cases, 670 were in Gentiles. Freeman (1947) reported seven cases in Negroes The etiology of the disease is unknown, but it is generally conceded that excessive smoking plays some part; there are now available several studies showing that peripheral vascular constriction accompanies the act of smoking Sulzberger, and Harkavy *et al* whose findings of some years ago were confirmed by Green (1942), independently arrived at the belief that there may be an allergic hypersensitiveness to tobacco in many cases; Westcott and Wright, however, did not share this opinion at the time they last committed [illegible]

[illegible]

Silbert (1945), rejected by Plotz after failing to find evidence of typhus antibodies in a small series of cases. Thompson (1944) believed that the cause might be hypersensitization to one of the dermatophytes. However, Silbert, who has had a vast experience in the treatment of this disease in the Clinic for Peripheral Vascular Diseases at the Mount Sinai Hospital, New York City, has very cogently remarked that since there is no known infection attacking almost exclusively one sex, as does thromboangiitis obliterans, it is extremely unlikely that this disease exists upon an infectious basis. He is firmly convinced that it is caused by smoking and is able to cite a series of 100 patients personally followed for more than ten years, all of whom stopped [illegible]

[illegible]

viduals constitutionally sensitive to tobacco; he furthermore says he has not encountered the disease in a non-smoker and that in his opinion reported instances of it in non-smokers are simply instances of faulty diagnosis.

The lesions show acute inflammation with occlusive thrombosis, organization

or healing, canalization of the clot, disappearance of inflammatory products, and the development of fibrotic tissue that binds together the artery, vein and

horizontal position and great redness (rubor) when it is dependent; coldness of the extremity; and lack of pulsation in the arteries affected. Migrating phlebitis of the superficial veins is of frequent occurrence. Ultimately, ulceration and gangrene occur in the great majority of cases.

Cohen and Barron's (1936) review of the autopsy literature revealed thromboangiitis obliterans as probably a generalized disease process that may affect vessels anywhere in the body. Hausner and Allen's (1940) observations at the Mayo Clinic substantiated this viewpoint 5.7 per cent of 500 patients had coronary involvement, 2 per cent cerebrovascular involvement, and there were three cases of abdominal and one of pulmonary involvement Rossier (1946), in Zurich, went so far as to say that the coronary arteries are as frequently affected as the vessels of the lower limbs, but I doubt that he will find many observers to agree with him. In 1942, Davis and Perret reviewed the literature and added four interesting cases of their own of the purely cerebral form; Scheinker (1944) also very thoroughly described a cerebral case.

THERAPY

This disease being of unknown etiology, of serious import, and as yet without a specific remedy, it is to be expected that a large number of remedial agents and measures shall have been tried. I shall discuss here only those that

the disease and last from a few months to several years, frequently as long as five, ten and even fifteen years. . . .Temporary arrests have been reported as

vealed that approximately 30 per cent of patients require an amputation within three years of onset of the disease, 40 per cent within five years and

varieties of therapy will occupy much more space than this, but nevertheless this is the most important of all the treatments.

Alcohol.—In contrast to tobacco, alcohol is definitely a dilator of the peripheral vessels. All observers use it freely in treatment of this disease, often proceeding to the point of keeping the patient mildly inebriated during a crit-

circulatory effects of alcohol, deplored the fact that these patients not infrequently become habitual drunkards.

Foreign Protein Fever Therapy.—Any of the fever-producing methods are employed, but principally typhoid vaccine. Wright's (1940) first dose is 5,000,000 organisms, and injections are given every three days provided that the effect of the preceding one has completely worn off. Increases of 3,000,000 to 5,000,000 organisms are made whenever the reactions are not satisfactory, decreasing by the same amounts if the temperature has exceeded 103° F. (39.5° C.) and a chill has occurred; with most patients the top level at which treatments have continued for long periods has been between 70,000,000 and 130,000,000 organisms. Treatments are suspended during acute infections or other serious illnesses. Freeman (1947) said that in the vascular centers of the Army during War II typhoid vaccine produced excellent results provided the patient had stopped smoking.

Sodium Chloride Intravenously.—The intravenous injection of 5 per cent aqueous solution of sodium chloride, introduced by Silbert in 1923, is the only one of the salt injection types of treatment that has held its own against all the other methods of treatment. The solution is prepared in freshly distilled water, filtered and sterilized at once. According to Silbert (1946), the initial injection is 150 cc., all subsequent ones 300 cc, taking about ten minutes for completion. The patients remain ambulatory and can get up at once after each injection; there are no reactions if the solution is properly prepared, though during injection the patient frequently feels very warm and thirsty. Injections are at first given thrice weekly, then twice, then at increasing intervals as improvement occurs. Duration of treatment—disappearance of symptoms or maximum possible improvement—is from six weeks to two years. Silbert (1946) reported that he had treated more than 900 patients during the past twenty-three years and that of this number over 800 had improved under treatment; in the great majority treatment was no longer necessary. He said that no patient restored to good condition had ever had recurrence of trouble or required amputation unless he resumed [illegible]

ulceration or massive gangrene were already present.

Desoxycorticosterone.—Sirota (1943) reasoned that a greater secretion of adrenal cortical hormone should increase the blood sodium chloride, increase blood volume and lower blood viscosity and therefore should, within limits, have the same effect as intravenous hypertonic sodium chloride solution. He therefore tried intramuscular injections of desoxycorticosterone acetate in dosage of 10 mg once or twice weekly for periods of one to seven months in a small series of cases; the results were sufficiently encouraging to warrant further study, but I have not seen a later report.

Other Agents Employed for Systemic Effects.—With due regard for the criteria of Perla, cited in the beginning of the discussion of therapy *in this* [illegible] the other systemically employed [illegible] iolyl, prostigmine, papaverine, [illegible] lium tetrathionate, doryl, and [illegible] or more is imperatively neces- [illegible] first seen, and when improve-

ment takes place the return to partial activity should be extremely gradual. [illegible]

electric pad or the electric bulb cradle, or by any other means through which heat at or slightly below the temperature of the body may be applied to the affected extremity continuously for a long period of time. Overheating will only increase the pain and is extremely likely to initiate the breakdown of the [illegible]

use of contrast baths and also wet dressings, but they employ sitz baths at about 100° F. (37.8° C.) for fifteen to thirty minutes once or more each day if there is no open lesion and soaking of the limb with an open lesion in physiologic saline solution at the same temperature. A warm cradle is employed to prevent chilling after these treatments. Wright, at the time he last wrote on the subject, was absolutely opposed to the use of heat lamps, diathermy or short-wave machines

Passive Vascular Exercise (Buerger Method).—Freeman (1947) said that the various types of passive vascular exercise were employed in numerous cases in the vascular treatment centers in the Army during War II but that the results were not striking. The original description of Buerger is still the [illegible]

amount of time necessary to produce blanching or ischemia As soon as blanching is established, the patient allows the foot to hang down over the edge of the [illegible]

are repeated over a period of about one hour, some six to seven cycles constituting a seance."

The number of seances per day varies for individual patients

Passive Vascular Exercise (Oscillating Bed Method).—In a few hospitals there are special beds in which in effect the Buerger exercises can be performed without any active participation on the part of the patient—the bed does the whole thing except pay the costs, which unfortunately limits the usefulness of the whole business.

Passive Vascular Exercise (Machine Method).—Landis and Gibbon (1933), and Herrmann and Reid (1933), independently devised apparatus for the treatment of chronic occlusive arterial disease through promoting peripheral blood flow by alternate suction and pressure applied to the affected extremity. The method has had enthusiastic trial, but the results in Buerger's disease

to say that the class of patient who profited most in their experience was the one still so little affected by the disease that he was unlikely to present himself for treatment. The apparatus is noisy and often causes the patient much discomfort.

Intermittent Venous Hyperemia.—Collens and Wilensky (1936) applied a pneumatic cuff to the proximal portion of the affected extremity to create *alternating periods of venous congestion and release. They described* excellent results in a large number of cases. Kramer (1939) reported good results in six of twenty-one patients. Wright (1940) and associates gave the method a thorough trial and then gave it up.

Peripheral Nerve Block.—For relief of pain the peripheral nerves are blocked by alcohol injection, crushing, or section with immediate suturing. This is in no way a specific treatment and is employed only as a palliative measure, but it is said to obliterate pain completely in nearly all instances; it does not relieve intermittent claudication. By the time regeneration occurs, in about a year, arrest of the disease will have taken place if the other elements of treatment *have been successfully applied Walking is not interfered with by these operations* (which are simply performed) but the wound surfaces become anesthetic and can therefore be painlessly cleaned and dressed. De Takats *et al.* (1939) finally dropped the crushing operation because of many anatomic variations, very painful paresthesias during the period of returning sensation, and [illegible] in the denervated areas. Perlow and Halpern

[illegible] 0's have been claiming considerable degrees of success with this operation. According to Hendrick and Aycock (1947), it will often prevent amputation for several years. Freeman (1947) *said that in the cases treated in the vascular centers* during War II, sympathectomy was the treatment of choice where there was clinical evidence of increased vascular tone; but good results were obtained only in patients who abstained completely from smoking

Treatment at Soap Lake.—At Soap Lake in the state of Washington there is a body of water claimed to have miraculous power for the cure of Buerger's disease. Allen and Kvale (1943) stated that Fatherree, who was director of the [illegible] Hospital at the Lake, was a former student and assistant of theirs [illegible] ording to [illegible] the water [illegible] *the rest,* the treatment there consists in baths taken in the water of the lake, varying amounts of rest and exposure to the sun, and daily dressing of the ulcerative and gangrenous lesions by the patients themselves, in addition patients fre- [illegible] of the ulcerative and [illegible] recur- [illegible] cent [illegible] had recurrent *attacks durin* [illegible] tion or both, prior to residence, [illegible] during their residence; 18 [illegible] on arrival and 68 per cent of these obtained healing in an average time of 8.5 months after arrival; 50 per cent of the patients had undergone amputation prior to their residence at Soap Lake and 31 per cent underwent amputation while there. Fatherree's conclusions were said to have been that the majority

of patients continued to have active manifestations of Buerger's disease after considerable periods of treatment at Soap Lake and that the treatment was not specific for the cure of the disease; however, he ascribed the popularity of Soap Lake to the fact that 66 per cent of all ulcerative or gangrenous lesions the patients brought with them to the Lake healed while they were there

VARICOSE VEINS

Varicose veins of the legs develop principally in women in the early child-bearing years, but in some instances they make their appearance at adolescence or at the menopause The incidence is much lower in men. The varicosities are usually only on the inner aspect of the calf and thigh and the inner and posterior aspects of the knee, but in advanced cases they are present on the posterior and outer aspects of the limb also They very rarely occur in the upper extremities

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doughy induration of the ankles Lymphedema, erythema and eczema are common, but the most serious complications are phlebitis and the sluggish chronic varicose ulcer that appears on the lower third and usually inner aspect of the leg and tends to attain very great size This ulcer is accompanied by marked inflammation and tenderness and has sloping edges and a coarse granulomatous exudate, in contradistinction to the luetic ulcer with its punched-out edges and serous exudate, and the tuberculous ulcer with undermined edges and a grayish necrotic exudate covering the base The subjective symptoms of varicose veins are a feeling of weight in the legs and dull aching pain, which is much relieved when the patient lies down or elevates the legs on a chair. Chapman and Asmussen (1942) offered evidence that circulatory efficiency is decreased by the pooling of blood in varicose veins and that undue fatigue, shortness of breath, dizziness, fainting and even precordial distress may be thus occasioned Spontaneous disappearance of the varicosities does not take place There seems to be an hereditary tendency toward development of the disease, but its real cause remains unknown.

THERAPY

Walking exercise favors venous return but standing is very bad for these patients. Great care should be taken to avoid even the slightest injuries to the legs as trauma favors the development of ulcer, but unfortunately just the class most often afflicted with varicosities, i e, the laboring class, can least afford to heed this admonition seriously The wearing of elastic stockings, or the employment of the woven elastic bandage of the Ace type, brings considerable relief to many individuals; tight garters and girdles should not be worn. The legs should be elevated during every moment that it is not absolutely necessary for the patient to be standing The reduction of obesity is probably of advantage.

CHOICE OF PATIENTS FOR INJECTION TREATMENT

The venous system of the lower limb is divisible into three parts: (a) the deeply situated femoral and popliteal veins and their tributaries; (b) the

superficial internal saphenous vein and its tributaries, serving the front and inner aspect of the leg and thigh and joining the femoral in the foramen ovale; and the short saphenous vein, coursing superficially on the back of the leg to join the popliteal vein at the upper border of the popliteal fossa; and (c) the communicating system of veins between the deep and superficial systems. Now since the substances used for injection of varicose veins provoke injury and adhesion of the vessel walls, *i.e.*, occlude the vessels, it is obviously of greatest importance to determine if the deep venous system is intact and functioning well before any part of the superficial system is destroyed. The method by which presence of full patency in the deep system is determined is called "Perthes' test": obliterate the superficial system with a blood pressure cuff over the foramen ovale and have the leg exercised; deep patency is indicated by emptying of the varices and absence of subjective symptoms, obstruction by dilatation of varices and pain. Injection treatment is not to [illegible]

to be bedridden; (3) saline solutions should not be used in nephritics, and *sugar solutions not in diabetics, otherwise, weighing each case with judgment,* such patients may be injected; (4) in cardiac decompensation, injection is usually contraindicated, (5) advanced age in itself is not a contraindication nor is peripheral arterial disease apparently, but in the latter cases the arterial rather than the venous disease usually demands preferential treatment; (6) pregnancy is not considered an absolute contraindication by all observers; (7) infectious processes anywhere in the body, even the common cold, contraindicate the treatments by common consent, but some men go so far as to include such a large list of focal infections as would practically eliminate three-fourths of the candidates, I should think; (8) neurotics stand these treatments, like everything else, very poorly; (9) to avoid the disaster that would probably attend injection of the lower limbs in the presence of thrombosis of the inferior vena cava, it is advisable routinely to scrutinize the abdomen for tortuous veins.

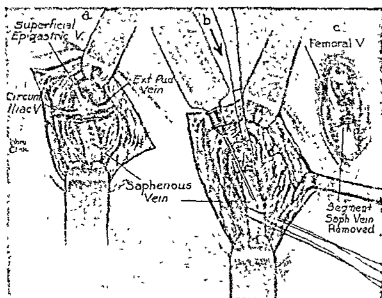
LIGATION PRELIMINARY TO INJECTION

Despite the enthusiasm for injection to the exclusion of all other methods of treatment, which has gripped the profession since about 1920, admission is being forced that recurrences are encountered with embarrassing frequency. [illegible] which the treatment [illegible]

saphenofemoral junction, such downward coursing blood will recanalize the sclerosed varix and dilate a collateral or redilate a varix below. Recognition of this fact is causing many conservative men to turn back to preliminary ligation of the internal saphenous vein at the saphenofemoral junction in selected cases, the basis of selection being a positive Trendelenburg test: lay the patient flat, elevate the leg and assist emptying of the varices by gently stroking toward the foramen ovale, then make pressure with the finger on the foramen and stand the patient up quickly; the varices will begin to refill slowly from below, but when the finger is released *filling takes place rapidly* with blood which is seen to shoot downward from above.

The technic of preliminary ligation and massive retrograde injection of the

upper saphenous system, as practiced at the Lahey Clinic of Boston, was described as follows by Swinton (1936), who kindly permitted me to use his illustration:



Method of performing a retrograde injection of a sclerosing solution into the internal saphenous system at the time of the ligation of the saphenous vein Note that all branches and the internal saphenous vein itself have been ligated before the injection is done (Swinton, N W: Surg Clin N. A, 16, 1723, 1936, by permission of author)

"The patients are admitted to the hospital the night before operation, the groin carefully prepared as for any surgical operation and usually the entire perineum shaved In many of the very obese patients it may be safest to continue this preparation for one to two days until the area is clean Many of these cases are done under local anesthesia yet we prefer in the good risk patients to use cyclopropane, as there is less distortion of the tissues and less discomfort to the patient A transverse incision is made parallel to Poupart's liga

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carefully identified the tributaries are divided. The main trunk of the saphenous is then ligated ½ to 1 cm from the femoral but not divided At this point we perform a retrograde injection of the entire system with one of the milder

sclerosing solutions. We believe this is also a distinct advance in the injection treatment. Varices in the thigh are frequently difficult to locate because of fat, the thigh in many women is very sensitive and we find that following the retrograde injection further injections into the thigh are seldom necessary. We employ a solution of 10 per cent saline combined with 30 per cent glucose for this massive injection. The amount required is variable but ordinarily 10 to 20 cc. is sufficient to obliterate all the veins down to the knee. We have used 40 cc. and thrombosed the entire saphenous system down to the ankle but we do not believe this is a safe amount. Following the retrograde injection a second ligature is placed on the saphenous 1 to 2 cm. below the first and the intervening section of vein removed. We feel that it is somewhat dangerous

operation the patients are urged to take a few steps each hour. After a general anesthetic this may be delayed a few hours but all patients have taken a few steps by the evening of the operation. Subsequent injections can be done at the convenience of the patient. . . .They may be started as soon as the patient is discharged from the hospital. There is probably slightly less discomfort if they are delayed a week following the operation. We have found that smaller amounts of the solution are advisable following preliminary ligation at each treatment than we used formerly when the vein had not been previously ligated . . . Many fewer injections are required where the vein has been ligated previously and most cases can be cleared up in 3 to 6 visits that formerly took two to three times that many injections. A word of caution should be said about discharging these patients We ask these patients to return for examination and tell them that 1 to 2 further injections may be necessary one month after the completion of the first series of injections, then three months later and again at the end of one year. Only in this way do we feel that all the varices will be found and obliterated"

I think the fact should be stated here that at least two men of vast experience in the injection of varicose veins, Isaak (1940) and Hayes (1941), expressed the opinion in no uncertain terms that the mortality is much higher following ligation and retrograde injection than following injection alone. If this is true, the general practitioner is in the safer camp for most of the ligations are still done by surgeons or specialists in peripheral vascular clinics.

Choice of Sclerosing Solution

Of all the large number of competing agents I shall include here only those few with which most experience has been had *Sodium morrhuate* has apparently most nearly filled the ideal requirements and has supplanted all other agents in a large majority of clinic and private practices. It is used in 5 per cent solution in a quantity of 0 3 to rarely more than 3 cc. at any one site. It causes very little pain on injection and severe and lasting after-pain in only an occasional patient; most of the Council-accepted preparations (1947) contain 2 or 3 per cent of benzyl alcohol as a local anesthetic. Sloughs are rarely reported as a result of injection outside the vein, and such as occur do not seem to be so serious as those caused by quinine. Occasionally the injection causes a reaction with thickening, tenderness and discoloration around the veins; this reaction,

reviewed by Vaughn and Lees (1942). But none of these systemic reactions is seen with great frequency. Weismann and Heyerdale (1941) suggested the injection twenty-four hours ahead of time of 0 5 to 1 cc. of this type of solution as a test dose, in the rare instances in which the patient manifests a systemic reaction the hypodermic injection of epinephrine will control the situation. *Quinine hydrochloride with urethane* is available in 2-cc. ampules, which is the top dose that may be injected in one site or at one sitting; the frequent occurrence of cinchonism would seem to indicate a 1-cc maximum as safer (immediate reaction. tingling, cyanosis, edema, bronchial spasm—antidote: epinephrine; toxic reaction, usually occurring after several hours tingling, neuralgia, vertigo, visual and aural disturbances, delayed reaction, after several days· malaise, itching eruption, fever, protracted course). Quinine does not cause injection pain or cramp or after-pain, but it does cause slough outside the veins. Schmier (1937) also charged it with being chief offender in production of the slough that sometimes appears several weeks following the injection of a thin-walled vein, a type of "postobliterative" slough which is said not to be due to perivenous infiltration Menorrhagia, premature menstruation, and bronze discoloration of the skin are recorded against the drug also *Sodium chloride* is used in 15 to 30 per cent concentration and in amounts from 1 to 10 cc It causes severe cramp on injection and slough outside the veins, but Schmier has known patients who preferred this brief cramp to the long drawn-out pain sometimes induced by morrhuate Some men, however, find the salt altogether too variable in its sclerosing effects *Invertose, sucrose* and *dextrose* are used in concentrations of 50 to 75 per cent and amounts of 2

Technic of Single Injection Method

Time has shown that there is no advantage in segregating a portion of the vein; the site is merely selected, the skin treated with an antiseptic, the needle introduced and the plunger withdrawn to be sure that the vein has been

tance of this cannot be overemphasized—and the patient instructed to indulge in no rubbing or massaging. Injections, usually made at intervals of one week, begin with the distal veins and work upward (except when there is ulcer—see later). Smith (1941) reported the average number of injections in a series of 491 cases as 8 per individual In the intervals between injections it is usual to keep a spiral elastic bandage on the limb; the patient is of course to remain ambulatory.

If it is suspected during the injection that fluid has escaped from, or been

placed outside, the vessel, injection must cease at once and 5 to 10 cc. of 1 per cent procaine solution should be immediately injected subcutaneously. The injection of 5 cc of the patient's own blood from a neighboring varix has

Latterly, the empty-vein technic has gained many adherents, McPheeters (1943) being perhaps one of its staunchest supporters. The steps are (a) apply a soft rubber tourniquet proximal to the site for injection with the patient standing; (b) then have her lie down and place the heel on a small block or box; (c) when entry is made the tourniquet is released and the injection made after the vein visibly collapses; (d) the limb remains raised until the elastic bandage is applied

Technic of Multiple Injection Method

In an attempt to shorten the total time of treatment many points along the course of a vein are injected at a single sitting. Horlick some years ago slightly modified McPheeters' original technic. His procedure is as follows: "The patient is placed in an erect position and the points where injections are to be made are marked with mercurochrome solution or tincture of iodine so that one may know where to inject when the veins are subsequently collapsed. The patient lies down and the extremity to be treated is elevated and stripped of blood. Two tourniquets are applied about six to eight inches apart, starting at the foot or ankle. These must not be applied so tightly as to cut off the deep circulation, for serious trouble might ensue from the sclerosing solution finding its way to a corresponding segment of the deep circulation. After this, the leg is lowered and the points previously marked are injected between the tourniquets with the solution to be used. Pads of gauze are strapped over each

groin. The most proximal of the tourniquets is left in place and the whole extremity is firmly and evenly bandaged from toes to groin. The Ace or

collapsed, as nearly as possible, by the bandage. The resulting thrombi will thus be smaller in diameter. It is advisable to keep the bandage in place until the next visit to the clinic. At the ensuing visit, small varicosed veins, so-called 'pick-ups,' missed at first, may be individually injected without the use of tourniquets. If the veins of both legs were varicosed and only one done at the first visit, the other may be done at the same time as the 'pick-ups.'" Horlick (1947) is inclined to feel that recurrence with the multiple injection procedure will eventually prove to be as great as with the single injection method; his approach to the problem of varicose veins has further altered to the extent that he now believes almost all the patients should have preliminary division of the saphenous vein.

Treatment During a Period of Phlebitis

The subject of thrombosis of the deep veins is separately discussed in Thrombosis and Pulmonary Embolism (*q.v.*). Until recently, most men in this field have been agreed that injection treatments should not be given in either leg while there is an active area of phlebitis present in one of them, the feeling being that an arbitrary waiting period of six months after subsidence is not a bit too conservative. Latterly, however, there have been a number of dissenters from this viewpoint. For example, Heyerdale *et al.* (1943), of the Mayo Clinic, stated that if the patient's symptoms are limited to a mild febrile reaction, dull pain, tenderness, redness and a sensation of stiffness in that portion of the extremity involved, the offending veins may be obliterated satisfactorily by a course of injections instituted at the earliest possible moment. In their practice preliminary ligation and injection are performed, warm, moist packs are applied to the affected extremity postoperatively for the patient's comfort for a day or two thereafter, and then she returns at suitable intervals for the further sclerosing therapy.

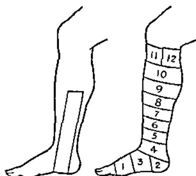
TREATMENT OF VARICOSE ULCER

When I was a hospital resident a certain number of years ago, we used to treat ambulatory cases in the clinic with salves and no hope, or an occasional Unna paste boot, but when we could get a bed in the house and a patient who could occupy it for the requisite number of weeks or months, we did cure her. The patient was put to bed, the ulcer cleaned, and a gridiron of narrow adhesive straps crisscrossed over it. Various wet antiseptic dressings were then applied continuously in the beginning, and later the exuberant granulations were cut down with the silver nitrate stick, which was also used upon occasion to touch up the sluggish edges here and there. They got well at last (shall I ever forget the old Irish woman who knitted sweaters for the staff, twice round!), but I do not think the dressings had anything to do with the result. The more blithely they went out, the more disgruntled they returned, however, for we were not doing enough with the recumbent position, and in those days we hadn't begun injecting the veins to attack the matter at its roots. Now all that is changed, for the majority of ulcers gradually heal after successful obliteration of the veins, and those that do not are apparently in most instances healed by one of the two bandaging methods described below.

The Occlusive Compression Bandage.—The advantages of this method, developed [illegible] up to date by [illegible]) the varicose [illegible] and thus reestablishing aeration of the tissues, (b) edema is reduced, thus bringing the edges of the ulcer closer together and pressing the raised margins of an indurated ulcer down flat; (c) delicate granulations and new epithelium are not only protected from dressing trauma, but the wound is actually dressed in its own secretions—the "pansement spécifique" of Besredka; (d) pain is abolished in the majority of cases; (e) work and exercise aid rather than hinder the cure; (f) cure is rapid—"frequently an ulcer of the size of the palm of the hand, if of short duration, will heal within seven days"; (g) the ulcer is cleaned more quickly than by antiseptic methods and fetor rapidly disappears; (h) varicose veins that had been deeply buried in edema are brought to the surface and rendered injectable; (i) the scar is supple without adher-

ence to the bones; (j) expense is saved; (k) no special training or skill is required to apply the treatment.

Details.—(1) The veins, if suitable, are injected concurrently with the treatment of the ulcer. (2) The leg is then wound with an elastic-adhesive bandage (elastoplast) very firmly and evenly, the tightness of the winding being proportional to the swelling and induration, sometimes using practically all of one's strength—"the almost invariable cause of failure is the looseness of the bandage." Begin winding near the toes, having first put in place the stirrup as shown in the accompanying sketch. Disappearance of the edema with the first bandage or two will loosen the support and necessitate reapplication and so too will copious discharge; the next bandage should be applied from above downward in order to eradicate the grooves made by the first. (3) If the ulcer is of the painful type, aspirin powder is blown in with an insufflator and the patient is given a hypnotic for a few nights, the latter not so much for the pain but because "she has fed the ulcer with salves, antiseptics, lint and gauze for so long that she thinks terrible things are happening under the bandage." The pressure over the ulcer, if it is a particularly painful one, is sometimes increased by applying a small firm ab-



sorbent felt pad to the ulcer bed and placing another pad of sponge rubber

it seeps through, with a nailbrush and soap, and to protect the clothing with a dressing over the weeping area, and also to wear a long stocking over the whole. *Work and as much walking exercise as possible are mandatory.* (5) Upon each removal of the bandage the veins are injected again in the previous order and also any others that have become accessible, and if the ulcer is large and a good sheet of granulations has developed, grafts are inserted under them on the fibrous bed—insinuation of small implants, darning in threads of skin, or injecting a suspension of skin in saline. "Grafting may be repeated and it is always well to have a graft waiting in the center of the last patch of ulcer to receive the edges as they close in, otherwise there is often an annoying delay at the last." (6) Finally, when the ulcer is healed and all veins obliterated, the former often being accomplished first, an Unna paste boot or an elastoplast bandage is used as long as seems necessary to consolidate the cure.

Wright considers associated arterial disease and diabetes to be practically

the only contraindications to the entire treatment, but he says that in some cases old-standing deep phlebitis with incompetency of the deep veins will render treatment of the superficial veins impossible or inadequate, and so a permanent support will be necessary. In the very worst cases an Unna paste bandage will be necessary for life. Wright says if these are carefully applied they will only need changing every six months

Rubber Sponge Supportive Bandage.—This method of therapy developed by McPheeters has been called by him the "venous heart" treatment and rests on the belief that the patient's heart will pump fresh arterial blood filled with oxygen and tissue food to the ulcerated area but that the circulatory apparatus must be artificially aided to carry off the products of combustion and ketosis which cause the local acidosis and tissue death To this end he applies a rubber sponge tightly to the ulcerated area and then causes the patient to walk a great deal, so that with each step the elastic sponge performs a "systole and diastole" by which serum, lymph and venous blood are actively pumped away from, and arterial blood into, the affected tissues at the same time that all the advantages of constantly applied firm pressure are obtained. Unless the patient exercises he will suffer intolerable pain; with exercise he will find that the normal soreness and the edema rapidly disappear and "ideal conditions are maintained for the ulcer healing, the end-results are reached in a comparatively short period, and the patient continues on at work during the entire period" McPheeters (1947) recently expressed himself as still very much pleased with the results obtained by the use of this treatment, it is to be understood of course that it is absolutely contraindicated in the bedridden

Details—(1) Cleanse the skin and ulcer area with gauze and benzine and apply 10 per cent silver nitrate to the ulcer, which will stimulate but is of no value at the first dressing of a badly infected and necrotic ulcer. (2) Apply some ointment that will *remain soft* to the ulcer, cover it with fluffed gauze and 4 layers of sheet wadding or cellucotton (3) Bandage in place directly on the ulcer a good grade rubber bath sponge (firmest possible) that is 1 inch larger than the ulcerating area, using a plain 3-inch gauze bandage and being careful that the whole does not slip to one side (4) Apply a 4-inch Ace bandage from just below the knee to the toes, over the sponge and dressing, applying it as a double figure-of-8 about the foot and ankle (5) Convince the patient of the absolute necessity of walking as much as possible (6) The dressings are to be changed as often as necessary to prevent saturation "Every two days is preferred. The rubber sponge can be boiled up and used again when soiled, but should be discarded as soon as it has lost its 'kick' and has become firmly pressed together" After healing, the subsequent treatment is practically the same as in the method of Wright (see above)

Local Application of Blood.—Following the lead of several earlier observers, Anderson *et al* (1946), at the Mayo Clinic, applied dried and powdered human blood cells, first cleaning the ulcer with wet dressings, then applying the powdered blood cells with a sterile spatula or swab or dusting them on from a container with a shaker top, then loosely covering with a dry sterile dressing The dressing was changed daily in the beginning and later only when there was evidence of exudate beneath that prevented contact between the cells and the bed of the ulcer. When healing was completed the crust was either allowed to fall off spontaneously or was soaked until it softened enough to peel off. Of course it is difficult to control a study of this sort, but it was the impression of

Anderson *et al.* that in approximately half of the patients healing was much accelerated by the use of the powdered blood cells. Orbach (1946) used a blood-kaolin-penicillin paste satisfactorily in seventeen of nineteen cases. The paste was very simply made by using the patient's own blood, adding to it kaolin in an equal amount, and then ½ cc. of penicillin solution (5000 units per cc.) to 10 cc. of the paste The paste was applied to the ulcer and covered with a sheet of gauze, a thick layer of talcum powder was then spread over the gauze and the entire leg encased in an Unna paste boot or an elastoplast bandage, the bandage being changed every five to eight days and the patient kept ambulatory if possible.

The Unna Paste Boot.—This dressing, several times referred to above, is made and applied as follows: (a) Stir 100 gm. of gelatin into 400 cc of water and allow to stand overnight; then bring to a boil and add 100 gm. of zinc oxide and 400 cc. of glycerin which have been previously rubbed together to smoothness; boil while stirring for fifteen minutes. (b) Cool to a bearable temperature, or heat to same if the paste has already hardened, and paint with a [illegible]

[illegible] that the ready-made zinc oxide-gelatin bandages, nowadays available, may be satisfactorily substituted in the above procedure. In the older type of treat- [illegible] window was cut over the [illegible]

above, the Unna dressing is more often applied on the dry surface after healing of the ulcer. When wet dressings are being applied, the boot is usually changed every two weeks, every three weeks at least

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ESSENTIAL HYPERTENSION

(Hyperpiesis)

In 1943, Master *et al.* reported a study of the blood pressures of nearly [illegible] cross-section of the [illegible]

inordinately high in the group, and the number of Negroes, in whom hyper- tension is appreciably more frequent than in whites, was much lower than in the total population—hence it was thought that if the figures erred it might possibly have been in the presentation of findings lower than those truly [illegible] population. The findings [illegible]

more [illegible] blood [illegible] ion of [illegible]

150/100 or over, about one-third of the male population and over two-fifths of the female population of ages forty and over have high blood pressure; this

percentage also rises rapidly so that it is present in more than a majority of men sixty and over and of women fifty and over. The study revealed such a high proportion of persons over forty with hypertension
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pressures below this level are more favorable for longevity.

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sixth decade. The assumption that diastolic pressure increases with age was shown in this study to be unfounded, for actually a progressive decrease occurs with succeeding decades and there is an increasing frequency of low diastolic levels (below 70 mm.) with

natural menopause, demonstrated that arterial hypertension was no more

several-fold in patients with hypertension—in their series the maternal mortality in 301 hypertensive pregnancies was 4 3 per cent, which was twenty times the general rate in their clinic. This study, however, did not confirm the supposition that pregnancy is remotely harmful to the hypertensive patient, for though

determinations of blood pressure were made

at the age of sixteen, corresponding diastolic pressures being from 52 to 62 mm.

The most exten
I h
of
mainly working men and women between forty and sixty-nine years of age, the age group fifty to fifty-nine predominating It would seem from Bechgaard's statistics that the prognosis in essential hypertension is by no means bad, for 41 per cent of the men and only 22 4 per cent of the women died during the period of observation, which was from four to seven years. In taking the normal mortality for the Danish population as 100 per cent, Bechgaard calculated the excess mortality in this hypertensive series as plus 168 per cent for men and plus 43 per cent for women The excess mortality was high up to forty-nine years and then decreased rapidly until seventy years was reached Unfortunately, however, in this study of Bechgaard he accepted as hypertensive a blood pressure which neither the British

nor ourselves would so accept, for he defined the upper limits of normal as 140 over 90 mm. Hg.

While the individual with hypertension often is broad-chested and obese he is by no means invariably so, for the lean and spare, the tall and pale-faced are afflicted with this disease as well. When he, or more often she, presents for examination, the symptoms leading to the discovery of the hypertension are usually disturbances in kidney function, cardiac and respiratory complaints, vertigo, dyspepsia, bleeding from the mucous membranes, loss of weight, retinal hemorrhage, persistent morning headaches, unusual drowsiness, and transient palsies and aphasia. The height of the systolic pressure varies greatly, and of course the height of the diastolic rise depends upon the state of the heart and vessels, hypertrophy and arteriosclerosis being usually early complications of hypertension. Patients are nowadays usually graded with regard to the severity of their symptoms as follows: Grade I, mild and variable hypertension with minimal eye ground, heart and kidney changes, Grade II, moderate and variable hypertension with slight changes in the eye grounds, heart and kidneys, Grade III, late benign hypertension but with the eye grounds, heart, kidneys and brain frequently showing involvement of considerable degree; Grade IV, malignant hypertension. Rogers and Palmer (1944) found that the transient nervous hypertension, frequently found during physical examinations in War II, had excellent prognosis at least so far as military risk was concerned, but Levy *et al.* (1945) concluded from their study of the medical records of 22,741 officers of the Army that this transient hypertension often represented an early stage of hypertensive vascular disease

The etiology of [illegible]
great strides have [illegible]
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associates being c[illegible]
it seems that the kidney produces a substance, renin, that is converted in the normal blood plasma into a second substance, angiotonin, the latter being an agent causing vasoconstriction (in the kidney there is particularly constriction of the glomerular efferent arterioles). There is also evidence that the normal blood contains a substance that inhibits the action of this vasoconstricting agent There has been much study of the effect of kidney extracts thought to contain the inhibitor agent, but the subject is still in the experimental stage and not ready for general application in practical treatment. However, the fact that unilateral non-nephritic kidney disease may give rise to hypertension seems to have been fully demonstrated The importance of heredity in hypertension is not fully elucidated.

THERAPY

Mode of Life.—Characteristically the hypertensive individual is a tense [illegible]

an extreme degree of insecurity in early childhood, with an unsatisfied dependent relationship to a threatening parent. To the psychiatrists—whose terminology and concepts we must learn to understand, like it or not!—it seems that, given this sort of bad start, the patient falters through life

out learning how to relax or to enter into any sort of secure and satis-
g relationships "Always," says Binger, "on the defensive, ready to fight
: afraid to fight." It would seem to be very important to understand
out these people that they are extremely rigid personalities whom it is
fficult to influence and hence to treat from the psychotherapeutic stand-
oint. To attempt deep and searching psychotherapy in such individuals
surely no task for the amateur since it will often give even the thoroughly
rained psychiatrist all he can handle. However, the common ordinary thing
of trying to provide reasonable rest and relaxation for a patient can certainly
be attempted by the average physician: the regulation of occupation, family
and social life, the advising of an after-lunch period of complete rest, in-
sistence upon at least eight hours in bed at night, etc If nervous relaxation
cannot be achieved without drugs, there should be no hesitation in employ-
ing sedatives—indeed, I know more than one competent internist who still
today believes that phenobarbital is unquestionably more valuable than any
other drug in use in the therapy of hypertension Some hypertensives find
that they are greatly relaxed by Turkish baths and therefore enjoy taking
them; but the physician must bear in mind that the relative hypotension
often suddenly induced by these baths may predispose to thrombotic oc-
clusion of vessels, depression of cardiac vigor and rebound of the arterial
tension to a level higher than before the bath I think it is the consensus
among students of this disease that the patient had best forego this indulgence

It seems that one may guardedly lay down the principle that exercise,
within the limits of cardiac power, is beneficial

There is no reason why the hypertensive patient should not travel at the
usual air line flight levels, but it must be accepted that cardiovascular com-
plications are contraindications to flight.

Alcohol in great moderation does not seem to be harmful, indeed it appar-
ently "smoothes out" some of these temperamental people Smoking is
sometimes demonstrably detrimental.

That a certain number of patients die in the lavatory is taken to mean that
straining at stool is to be combated by the use of cathartics or enemas; be
it noted, however, that no one has proved this point

Diet.—All the dietary restriction that the hypertensive patient needs is in
quantity if he is obese or if there is a gobbling fulsome tendency in his family;
for every bit of evidence in favor of any particular *qualitative* change in diet
it is possible to find a sufficient amount of recorded contrary evidence to
invalidate the whole contention. However, that one may expect abstemious-
ness to be helpful was shown in a paper of Lups and Francke (1947), who
found clear evidence that starvation has a salutary effect upon blood pressure.
These workers studied the blood pressure readings of 520 persons before the
period of starvation began in Utrecht, Holland, during War II and after
the liberation and return to a reasonably good dietary It was evident that
during the severest hunger period the average pressures, both systolic and
diastolic, were definitely lowered; furthermore, when considerable weight
was lost by an individual the pressure was more often lowered if he was
hypertensive than if he was hypotensive

Venesection.—Bleeding as the sheet-anchor of treatment has of course been
abandoned but many physicians still resort to it in the plethoric individual
when heart failure or apoplexy is threatening Edwards and Bordenave (1946),
in a study at one of the American Red Cross Blood Donor Centers during War

II, in which they employed sixty hypertensive blood donors as subjects, found that in the hour following bloodletting there is a considerable rise in the systolic pressure, which they felt should be accepted as a warning against indiscriminate bloodletting. However, they observed that in about 95 per cent of their subjects there occurred a gratifying drop in blood pressure about one week after withdrawal of 500 cc. of blood; this would seem to justify venesection as a therapeutic procedure since in addition to the fall in blood pressure there was a very noticeable feeling of well-being experienced by most of these people. It was found that at the end of eight weeks blood pressure was usually back to its pre-donation level or higher, but meantime the patient had been provided with several weeks of symptomatic relief

Intravenous Injection.—The modern method of depleting the circulation and thus relieving the brain is to inject hypertonic solutions, but the superiority of this method to venesection does not seem to me to have been conclusively shown. *Sucrose* in 50 per cent solution is injected intravenously in an amount of 300 to 500 cc. daily. It seems that diuresis begins in two hours and lasts usually

must be done very slowly in patients with any type of cardiovascular complication.

Spinal Fluid Drainage.—Kerr (1946) said that in a considerable proportion of patients who have increased venous pressure and in whom encephalopathy, cardiac failure and some renal failure are developing, he has found the spinal fluid pressure to be very high. Frequently-repeated withdrawals of as much

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cated Weaver *et al.* (1944) found that some of their patients on mannitol hexanitrate obtained striking relief of symptoms even though the drug had

blood pressure, but it
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mic tablets that are not volatile, do not quickly deteriorate and may be easily dissolved under the tongue. The dose is one or more 1/100 grain (0.6 mg.)

tablets as required. The drug is cheaper than the erythrol or mannitol salts. Lueth and Hanks (1938) reported severe reactions in a number of their patients using nitroglycerin; nausea, vomiting, collapse and the involuntary passage of urine.

Amyl nitrite is not used in the treatment of hypertension because of the brief duration of its action.

Evans and Loughnan (1939), in the study referred to under Iodides above, found bismuth subnitrate effective in inducing symptomatic, though not blood pressure, improvement; the nitrate radical is liberated as nitrite by bacterial action in the intestine and the nitrite slowly and evenly absorbed. Usual dosage is 10 grains (0 6 gm.) three times daily in capsules

Thiocyanates (Sulfocyanates).—Hines (1946), of the Mayo Clinic, in a paper designed to establish the present status of thyocyanate therapy, raised and answered certain questions as follows: What is the pharmacologic action of thiocyanate? This has not been satisfactorily explained. Do thiocyanates lower blood pressure? This question is not settled to the satisfaction of all investigators. Do the thiocyanates relieve symptoms due to or related to hypertensive disease? Almost all investigators agree that the majority of patients who have no marked unpleasant toxic effects from the drug experience considerable or complete disappearance of symptoms such as headache, vertigo and nervous tension However, a well controlled study on a large group of patients has not yet been reported. How is the administration of thiocyanate controlled? Dosage for the individual patient may be controlled easily and accurately by the periodic determination of the level of thiocyanate in the blood. What preparations of thiocyanate may be used and what is the method of administration? Either sodium or potassium, but more frequently the latter, thiocyanate is employed in solution (with peppermint water as preferred vehicle) or as enteric-coated tablets, the latter being the usually preferred preparation. What is the dose of the thiocyanates? The dosage at first should have as its aim the establishment of a thiocyanate level in the blood of between 8 and 12 mg. per cent; then if satisfactory results are obtained at this concentration the dosage may be so decreased that a level of 4 to 6 mg per cent is maintained in order to avoid as much as possible unpleasant side effects; however, in some patients it will be found necessary to maintain the level at about 12 mg. per cent for satisfactory effect. If there is no evidence of renal insufficiency [illegible]

an initial dose of 12 grains (0.75 gm.) daily, the first determination should be made not later than the seventh day and subsequently every week or ten days until the maintenance dose of the drug has been determined; for smaller initial dosage the first determination may be postponed until the tenth day and determinations should then be performed subsequently at the same intervals as for the greater initial dosage. Even after a stable maintenance dose has been calculated the level should be determined at least every two or three months as long as the patient takes the drug. What are the toxic or untoward effects to be watched for? Many patients experience mild degrees of lassitude and weakness even when the thiocyanate levels in the blood are within the so-called safe

therapeutic range. If the use of the drug is persisted in, these symptoms usually cease to occur or to be annoying after a few days or weeks. However, if severe degrees of exhaustion and weakness occur, as they may occasionally, and persist for more than a day or two, it is best to discontinue the attempt to use the drug. In about 5 per cent of instances skin eruptions occur about a week or ten days after the beginning of treatment; treatment being discontinued, it will be found that the eruptions clear up within a few days and that in about half the patients they do not recur on resumption of administration within a week or ten days. Exfoliative dermatitis is a rare occurrence. Purpura occurs occasionally and if of more than mild degree probably warrants discontinuance of the drug. Nausea, vomiting and marked weakness are among the significant signs of beginning severe toxic reactions. Mental disturbances occur commonly in these severe reactions, ranging from mild drowsiness and lapses of memory to signs of severe psychosis with hallucinations and disorientation; these symptoms of a severe and sometimes fatal reaction should not occur if the proper precautions have been taken and if the drug is discontinued when mild symptoms of toxicity appear. Occasionally the so-called cyanate goiter may develop, accompanied by symptoms of mild or severe hypothyroidism; this picture clears when desiccated thyroid is used in appropriate doses whether or not the administration of thiocyanate has been discontinued It seems impractical to use iodides routinely for prevention of this rare occurrence. In occasional instances osteoporosis associated with moderate to severe pain may be observed, but the pain subsides and the osteoporosis usually disappears when treatment is discontinued. What are the contraindications to the use of thiocyanates? "(1) Moderate or severe degrees of renal insufficiency; (2) arteriosclerosis of the central nervous system or moderate or severe degrees of organic disease of the central nervous system of any type; (3) blood dyscrasias, especially thrombocytopenic purpura; (4) somnolence or coma from any cause; (5) history of severe degrees of sensitivity to drugs; (6) inability of the patient to have determinations of the level of the thiocyanate in the blood made at

treatment of hypertension are not agreed upon, some men using the drug in any patient with a moderate or severe degree of hypertension who does not

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above may certainly do so without fear of hindrance from any man.

Lumbodorsal Sympathectomy.—In the preceding edition or two of this book I felt it my duty to express the very skeptical attitude I had toward sympathectomy for the treatment of hypertension—a purely "arm-chair" opinion, to be sure, but one formed as the result of an earnest study of the vast literature of the subject and of conversations with many men here and there and round about. Now, however, with the more radical procedure of lumbodorsal sympathectomy having been performed a great many times by fairly large numbers of surgical groups, I moisten my finger and test the wind and find it charged with a considerable enthusiasm—Paul D. White was almost ecstatic when he came out here to discuss the matter before us in late 1946—and I therefore feel it incumbent upon me now to attempt a comprehensive

presentation here of what the surgeons think they can do with this new operation Perhaps the obligation should be considered all the more pressing since, as some editorialist has recently pointed out, internal medicine has snatched many a patient away from the surgeons in recent years with sulfonamides and penicillin I shall not attempt to review the great mass of literature that is now available on this subject, but for the sake of simplicity as well as in an attempt to present the matter in the fairest light possible to the surgeons, shall condense and summarize here the medical evaluation of the surgical treatment of

currently employed surgical procedures

Summary of Three- to Five-Year Follow-up of Patients —In the evaluation of results in surgically treated patients, Palmer considered that those who were dead in three to five years can certainly be considered unsuccessfully treated, and that those still living and with normal or near-normal blood pressures after at least three years could be considered successfully treated Upon this basis he reviewed sixty-eight patients and found that twenty-one of them were dead and therefore failures, that sixteen of them had normal or near-normal pressures and therefore were successes, and that thirty-one of them had continued to be hypertensive or had returned to the hypertensive state—in this latter group of patients Palmer considered the result "doubtful" or "equivocal," but I do not understand what he considered doubtful about the status of these individuals

Choice of Patients for the Operation —Palmer considered that there are no positive tests or categories by which success or failure may be predicted accurately in an individual patient He felt that in general it is probably true that the younger the patient (preferably under the age of forty), and the less the evidence of organic change, the better the chance of an excellent result, the chances of women appearing to be better than those of men, probably because the disease in them is generally more benign. He said that the pattern of the blood pressures in these patients seems to make little difference except that extremely high diastolic pressures are associated with more pronounced organic changes He felt that a spontaneous fall of the blood pressure to near normal while at rest in bed is evidently a favorable sign, and yet the patients who respond in this way to bed rest may be uninfluenced by operative intervention; he felt also that with the sedative test a fall to normal is found less frequently in those who may be expected to die, but about as often in those who remain or again become hypertensive as in those impressively benefitted in respect to their blood pressure levels. The effect of the grade of the disease upon the result of surgical therapy by this method seems to have been rather sharply shown, since 75 per cent of those successfully treated had Grade I or II hypertension, though among the successes was one patient designated Grade III because she had actual heart failure; and another important observation was that three patients with malignant hypertension were successfully treated (none of the three, however, had evidence of renal impairment

normal or near-normal, later the figure was 50 per cent, then 40 per cent and

at the time of his report approximately 25 per cent (sixteen of sixty-eight patients) in patients *followed three years or longer.* However, Palmer said that the blood pressure is more effectively lowered, even if only temporarily, by surgical than by medical treatment (his statement being based upon the comparison of forty-nine patients treated surgically and forty-three closely watched medically, *both groups of patients being outside the series under* present consideration) in mild and moderate benign hypertension (Grades I

after the operation, especially after both sides are done, there occurs a deep and sustained fall in blood pressure usually requiring elevation of the foot of the bed and the administration of parenteral fluids, including blood, and of neosynephrin intravenously. The recovery from this initial severe hypotension usually takes place in two to five days but it may require longer; thereafter, sitting upright or standing may cause prompt disappearance of the blood pressure in the arm, an exceedingly rapid pulse, breathlessness, decided blanching, often coldness of the upper extremities and unconsciousness—in short, orthostatic hypotension with vasomotor compensatory adjustments. Palmer said that a tight elastic abdominal binder and tight elastic bandages on the legs will ameliorate or prevent these changes, especially if there is accompanying muscular activity (walking), and that they become progressively less in the course of one or two months but may be recognized *in some cases as long as two or three years after the operative intervention.* Tachycardia, breathlessness and a lightheaded feeling often are noted months or years later when the subject has climbed a flight of stairs and pauses. Palmer said that raising the head of the bed during the hours of sleep reduces the *intolerance noted more especially on arising in the morning,* and that most patients (though not all) can do without leg bandages in a few weeks and without an abdominal binder in two or three months.

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intervention Palmer said, however, that there are certain patients with some loss of cardiac reserve who may show additional signs of failure while awaiting operation, or between the two stages, but who show remarkable clearing of all signs of failure and no longer require digitalis after the second stage of
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Complications of the surgical procedure are the relatively commonly seen extrapleural fluid, the fairly commonly seen basal atelectasis, and the infrequent pneumothorax. Palmer said that these conditions are usually dealt with easily, but that postoperative pain in the back and neuritis are common and sometimes persistent occurrences requiring the use of salicylates or

codeine or even demerol, hot fomentations and counterirritants. Such backache or pain in the flank may last several weeks or months and may be annoying for a year Six to ten weeks of hospitalization are required for this operation, another six weeks to two months of convalescence, and nine months to a year before the patient can expect to feel perfectly well. The relative postural hypotension with the compensatory phenomena of tachycardia and breathlessness may be disabling for months. It would seem that the operation may precipitate or definitely aggravate the occurrence of Raynaud's disease Other complications noted by Palmer are indigestion and

that perforation of or bleeding from a peptic ulcer may occur without a clear-cut clinical picture. It seems that some of the patients are also plagued by recurrent pyelonephritis. The effect on libido and potency in men is said to be diffi-

Palm

tality,

For

opinion the one condition in which dorsolumbar sympathectomy not only is effective but is also the only hope of palliation is Grade IV or malignant hypertension, but only if renal or cardiac impairment is not severe and as a rule if frank heart failure is not present.

To Whom May Sympathectomy Be Offered?—Palmer's answer is that sympathectomy may be offered to patients with Grade I and II hypertension (see the beginning of this article for delineation of these grades). He said that it should be especially offered to these patients if interval observations show that the actual levels of the blood pressure are growing worse, since he had

few women at or just after the menopause in whom there develops a severe vasospastic state with hypertensive crises, who may be much helped. Palmer said that in hypertension coming on in middle life in men, especially if brought to light by clinical evidence of arterial or arteriolar disease in the brain, the heart or the kidneys, the operation does not seem as yet to be so certainly beneficial; the progress of the disease in this group may be delayed by the relative postural hypotension produced, but the diffuse arteriolar disease is not helped

formed by Smithwick and his group is not the only operation of this sort that is being done. Some men are doing even more radical sympathectomies, and Peet (1947) is apparently getting good results with his bilateral supradiaphragmatic splanchnicectomy that is a somewhat less extensive denervation than that performed by Smithwick. But I cannot of course devote these pages to an analysis of results from all of these variations There is, however, another operative procedure that requires consideration here, namely unilateral nephrectomy, which has as its goal the removal of a kidney that may

be causing the hypertension in the sense of Goldblatt (see opening description in this article). It would seem from the literature that this operation has been performed in the hope of relieving hypertension in the presence of almost every type of surgical kidney. The study of Ratliff *et al.* (1947), at the University of Michigan, showed that hypertension may coexist in any of the common renal lesions but that there is no consistent relationship between hypertension and any particular gross renal lesion. In their pyelographic study of approximately 1350 patients, made solely in an effort to determine a possible renal [illegible]

[illegible]

for he found that only about 2.5 per cent of all the hypertensive cases studied at the Mayo Clinic had clinical or roentgenographic evidence of unilateral surgical renal disease and that less than 0.5 per cent of all hypertensive cases were suitable for nephrectomy as a cure for the hypertension. In Wattenberg's (1 [illegible] was less [illegible] reviewing [illegible] countered in unilateral renal disease is no higher than the incidence in a control group of a comparable age taken at random.

In the group of forty-nine patients with severe hypertension nephrectomized by Ratliff *et al.* the results were said to have been good in 34.6 per cent, but nothing was said about the length of the follow-up period except that it had been longer than twelve months in all but eight of the cases. But numerous observers have pointed out that almost any sort of major surgical procedure may result in a considerable lowering of the pressure in hypertensives for a year or more. Sensenbach (1944) was able to find only five cases in which nephrectomy delivered a successful result after two years, though to that list should be added the subsequently reported case of Kennedy *et al.* (1945) with relief of five years' duration, the case of Hyman and Leiter (1945), three years' duration, one of the cases of Ratliff *et al* (1947) of nearly seven years' duration, Seman's (1944) case with a duration of three years, the case of Wattenberg (1946) of three years' duration, and Carroll's (1946) single case with a duration of six years Kittredge and Brown said that of those patients who require nephrectomy for well-established unilateral renal disease only a small percentage can expect relief from any coexisting hypertension. It would seem, too, that in considering this operation one would do well to bear in mind one of Sensenbach's (1944) conclusions, namely, that the removal of a kidney if it retains any function at all is likely to increase the severity of the hypertension rather than to improve it, this being true even though the function of the opposite kidney is entirely normal.

Roentgen and Pitressin Therapy.—Pendergrass *et al.* (1947) feel that in some cases of hypertension there is an increased activity of the pituitary gland, and that for clinical purposes it may be assumed that subjects with hypertension who show increased production of antidiuretic hormone also have an excess of pressor hormone, the production of which they believe to give rise to the hypertension. This group has irradiated the pituitary region as a treatment for hypertension in 142 patients without untoward effects, [illegible] showed severe acute but transient [illegible] the [illegible] ty-

six months, averaging sixteen months, and about half of these were said to have showed improvement in blood pressure and clinical condition Further extensions of this work will be watched with interest, particularly since Griffith *et al.* (1946) seem to have had some success with the intramuscular injection of pitressin tannate, 1 cc. weekly for three weeks, then monthly for three months, and thereafter at monthly intervals until the bioassay for antidiuretic hormone became and remained negative. The rationale of these pituitary approaches is certainly difficult to establish, but perhaps one cannot quibble over such a point as the therapy of hypertension stands today.

ARTERIOSCLEROSIS

Arteriosclerosis is a disease characterized by hyperplastic, hypertrophic, fibrotic, calcareous and necrotic changes in the vessel walls, resulting ultimately in diminution of normal elasticity plus weakening and deformity. Apparently many individuals can remain in excellent general condition with tortuous and quite "hard" arteries, but they carry always the potentiality of [illegible]

and physical vigor in an elderly individual otherwise apparently healthy is looked upon as presumptive evidence of generalized arteriosclerosis; (b) if ophthalmoscopic examination reveals normal or nearly normal retinal arteries, and if there is extensive drop in diastolic blood pressure upon inhalation of [illegible]

arteriosclerotic or thromboangiitic occlusive involvement in the extremities.

In most cases the blood pressure is not raised, but when it is, that is to say, when essential hypertension and arteriosclerosis are coexistent, then the prognosis is much more grave. The following is the order of frequency with which most pathologists have found the organs to be affected, those organs most frequently affected being also most markedly affected: spleen, brain, kidneys, [illegible] lungs, liver [illegible] that at au- [illegible] number of [illegible] in the brain without a history of happenings to correspond with those lesions. He is trying to interest the profession in recognition of the fact that one of the commonest ways of "petering out" is that in which the brain is slowly destroyed by the repeated thrombosis of small sclerotic blood vessels, pointing out that many bizarre episodes as unlike as gastro-intestinal upsets and marked changes in character can be the expression of small strokes of this sort.

Some investigators are beginning to state in a tentative fashion that a definite hereditary factor is responsible for the development of arteriosclerosis in some individuals much earlier than in others living under the same stress and strain. The numerous reports during and subsequent to War II of the occurrence of arteriosclerotic vascular episodes in young soldiers

indicate that arteriosclerosis is not perhaps merely the inevitable consequence of senescence but the result of the action of some factors upon the vascular tissues at least to some extent independent of age. Diabetes appears with suggestive frequency in connection with this disease, but what direct relationship it or any other factor such as the alleged disturbance of cholesterol metabolism has to do with the etiology remains unknown. To those especially interested in the subject of arteriosclerosis the fine review of Hueper (1944-1945) is heartily commended.

The great anatomist Scarpa (1747–1832) was the first to record the opinion that arteriosclerosis is a disease of the inner coats of the arteries.

THERAPY

For those victims of arteriosclerosis who suffer general mental and physical deterioration there is nothing to do save direct their lives in as pleasant channels as possible; nor can one write much of an edifying nature about the prevention of the condition. To avoid the competitive hurly-burly of life as much as possible, to avoid too quick returns to full activity after attacks of the acute diseases, to submit to the fullest treatment for the chronic affections, and to select one's parents as carefully as may be, are all measures of presumptive value. No form of dieting, not even that type called "low-cholesterol" (omit brains, butter, egg yolk, fish and fish roe, kidneys, lard, liver, meat, oysters, poultry, suet and sweetbreads) is rationally indicated. In effect the treatment of localized arteriosclerosis is really the treatment of chronic nephritis, coronary thrombosis, congestive heart failure, hemiplegia, etc.—entities dealt with elsewhere in the book. Where there is intermittent claudication and peripheral vascular occlusion with gangrene, the treatment is essentially the same as in thromboangiitis obliterans, except that elderly arteriosclerotic patients may be expected not to tolerate typhoid vaccine injections so well as the younger patients with Buerger's disease. According to de Takats and Evoy (1947), lumbar sympathetic ganglionectomy may be indicated in a case of arteriosclerotic disease of the lower extremities; it seems that this operation will result in persistent vasomotor paralysis and thus aid in increasing the local blood supply. It was said that in one group of patients there was a dramatic increase of walking ability, that in a second group amputation was averted, that in a third group intractable neuritic pain of the causalgic type was benefited, and that in a fourth group amputation could be performed at a lower level.

Gubner *et al* (1947) reported that they could augment peripheral blood flow of the vessels of the toes, fingers and forehead by availing themselves of the specific dynamic action of aminoacetic acid (glycine, one of the amino acids) to increase heat production in the body. Twenty grams of glycine dissolved in 200 to 300 cc. of water or milk (and later in flavored agents supplied

water or milk

in twenty-six

oes occurred in

three of four patients and blood flow to the extremities was found to be increased in four of five patients; but an increased oscillometric pulsation in the calf in three such patients could not be observed. This experimental study is extremely interesting and it is hoped that something of practical clinical importance will come of it.

Doane and Adlin (1944) reported one case of intermittent claudication

relieved by thyroidectomy, but it is not often that a single swallow has made a summer. Bernheim and London (1937) found cessation of smoking equally demanded in the peripheral vascular occlusion of both arteriosclerosis and thromboangiitis obliterans It is possible that in arteriosclerosis one or other type of passive vascular exercise may finally be shown to be of somewhat more value than in thromboangiitis obliterans, but so far I have seen no published study proving this to be so in a large series of cases Gootnick (1943) obtained complete relief from the severely painful calf muscle cramps that often afflict arteriosclerotic patients in bed at night by the administration of quinine sulfate at bedtime, 3 grains (0.2 gm.) usually sufficing, Nicholson and Falk (1945) also found the employment of quinine helpful These cramps may often be prevented by the simple device of avoiding extension of the foot when stretching

HEMIPLEGIA

The three chief causes of hemiplegia are hemorrhage, embolism and thrombosis, but it will be convenient to include at this place also a few measures more particularly applicable to cord bladder resulting from paraplegia due to severe cord injury or as occurring in the tabetic. Whether the patient has bled or is bleeding at the time he is first seen in a typical "stroke" is by no means easy to say, but it is the time-honored custom to assume that hemorrhage is occurring and that something must be done to stop it To this end it is usual to place an ice-bag on the head and lower the feet and place them in a warm mustard bath; if the latter measure is not easily feasible the feet should at least be warmed by the use of hot water bags or the electric pad. Most patients who have bled sufficiently to have hemiplegia will die very soon and these measures will probably do nothing to stay the end; however, it is little short of cruel to the anxious family merely to stand by and do nothing, and thus these manipulations are amply justified on the basis of the activity and pa[illegible]
ty [illegible]
a [illegible]
cu [illegible]
bl [illegible]
lu [illegible]
[illegible]

patient has [illegible]

[illegible]
water bath The best way to minimize the damaging effects of sustained pressure upon bony prominences is to have the patient shifted from one position to another—every two hours is not a bit too often. Water cushions, next best

air cushions, and lastly cotton rings, placed to advantage, will help distribute the pressure; pillows under the back and knees are also helpful. Sheets and [illegible]

[illegible] in the nursing by pulling on a rope to raise the upper part of his body, special attention must be given to the skin of the buttocks and lower limbs that is much chafed by such movements. In most instances frequent gentle rubbing of the back with 50 per cent alcohol (not denatured), followed [illegible]

[illegible] excessively dry, will be better treated by the application of an ointment; Fantus (1935) offered the following, which looks very much like a shotgun prescription to me despite its alleged popularity with the nurses at the Cook County Hospital.

℞	Zinc stearate	5.00
	Tincture of benzoin	5.00
	Scarlet red ointment, 5 per cent	0.25
	Hydrous wool fat	30.00
	Liniment of camphor	180.00

[illegible] mixture is secured.

Label: After each cleansing, apply a very small amount of this ointment during the back rub if the skin is harsh and excessively dry (to prevent bed sores).

The application of elastic adhesive plaster (elastoplast), not stretched before applying, or a dressing of flexible collodion to a threatened point is said to prevent sometimes the development of a bed-sore. The greatest difficulty lies of course in preventing maceration of the skin in a patient who is incontinent. Several layers of newspapers on top of the sheet (which has a rubber sheet beneath it to protect the mattress), with absorbent material such as oakum between the papers and the body, is the measure usually resorted to; sometimes such a dressing may be held in place diaper-wise. In the worst cases a specially divided mattress may be employed, or a hole may be cut in the mattress at hand and the fluids directed into a pan on the floor by rubber sheeting draped in the hole. [illegible]

and the whole "bed" can be stirred up daily with a paddle to keep it soft and comfortable. Softwood sawdust is of course to be chosen and walnut especially avoided because it stains when the patient perspires.

Treatment of Bed-Sores.—Lamon and Alexander (1945) reported the closure of several bed-sores with the aid of penicillin given both parenterally and locally: the patient having received 100,000 units of penicillin intramuscularly for twenty-four hours, each of the wounds was carefully excised

and the granulation tissue in the bed of the ulcers was removed *en masse* with the skin edges, 20 cc. of penicillin solution containing 250 units per cc. were injected copiously into and around each wound, and the wounds were then closed in two layers with interrupted sutures of number 40 white cotton (with the exception of one ulcer in which it was necessary to use a slightly heavier grade of braided silk); except for the extrusion of four of the silk sutures there had been no breakdown of the wounds in the three months which had followed the closure at the time the report was made White *et al* (1945) also reported a small series of cases successfully treated in this way. Downing *et al.* (1947) reported good results with furacin soluble dressing in the treatment of three cases In the case of a non-hemiplegic patient who was suffering excruciating pain from a large bed-sore, Allen *et al.* (1946) injected a solution of 60 grains (4 gm.) of procaine in a liter of 5 per cent dextrose solution intravenously at such a slow rate that it lasted ten to twelve hours; the pain was completely controlled.

When slough has separated or been curetted away and "stimulant" treatment seems indicated, the time-honored therapy is to use on alternate days the N.F. scarlet red ointment and a dressing of equal parts (more or less) of balsam of Peru and castor oil. The experience of Vorhaus *et al.* (1943) in a few cases indicated that the healing of bed-sores might be promoted by the systemic administration of vitamin B complex.

Care of the Bladder.—If there is paralysis of the bladder every effort should be made to prevent overdistention with consequent dribbling and great danger of maceration of the skin on the one hand and urinary tract infection on the other. But no catheterization, not even the first, should be made under any but the most absolutely aseptic conditions Catheterization at six-hour intervals is the frequent practice, but the urologic profession seems to be divided on the question of tidal drainage versus chemotherapeutic agents to prevent infection. The employment of solution G (see Stone) is often of importance for the dissolution of stones. According to Emmett (1947), transurethral resection of the vesicle neck has been found to be an important therapeutic procedure for chronic cord bladder in that through it a mechanical defect is corrected and the patient is taught to substitute the use of intact muscles for the use of muscles that are paralyzed

Care of the Bowel.—It is customary to give a daily enema, preferably of sodium bicarbonate instead of soapsuds, and to leave the patient on the bed-pan for an hour afterward so that all of the slowly returned water may be caught. Some men [illegible]

Combating Dehydration.—In many instances it would seem advisable to give one or more 1-liter infusions of dextrose-saline daily, until the patient is able to swallow satisfactorily For the promotion of comfort it is also important to maintain the mouth in a moist state; Freeman (1941) wrote of the use of a water bottle with a gauze wick leading down into the patient's mouth to deliver water sufficiently slowly so that the occasional reflex swallowing would take care of the situation

Combating Muscular Spasms.—The exceedingly distressing sudden painful spasms of the paralyzed limbs that occur reflexly in some instances when the cord has been severely damaged require the use of large doses of sedatives

Doane *et al.* (1947) reported a case in which the *administration of 1/4 grain* (15 mg.) of prostigmine bromide and 1/2 grain (30 mg.) of phenobarbital four times daily s [illegible]
of motion and d [illegible]
condition; of co [illegible]

Massage and Faradization.—In recent years there has been a trend away from routine employment of massage in hemiplegia; it is also felt nowadays that electrical stimulation of the muscles with faradic current is not only useless from the standpoint of reestablishment of nervous pathways but is actually harmful in that it goads into further spasm muscles that are already spastic.

Exercise.—Practice has moved away from sole dependence on passive movements; indeed, Hobhouse (1936) probably expressed the consensus when he said that in hemiplegia the only passive movements necessary are full movements of joints to maintain mobility and ensure positions of the limbs that will not permit the formation of deformities. On the other hand, everything possible should be done to begin active movements from the very start, before the initial flaccidity has been replaced by spasm Attempt must be made to [illegible] during [illegible] some- [illegible] n itself provides a stimulus for movement and it is less to be feared than apathy." Metcalf (1934) recorded that in the return of muscle activity after his own stroke there seemed to be a threshold of resistance that had to be overcome and that this threshold lessened in successive trials on any one day and from day to day. Hemianesthesia may impede recovery but it does not seem to necessitate modification of treatment. Expecting a patient to be constantly [illegible] sound one at his service [illegible] n of the sound one [illegible] other. Right hemi- [illegible] to be accompanied [illegible] 'ound the prospect of motor recovery decidedly better when the right side was affected.

ECLAMPSIA AND HYPEREMESIS GRAVIDARUM

ECLAMPSIA

Eclampsia is a disturbance of pregnancy characterized in the end by convulsions, coma and a high death rate, and nearly always recognizable some [illegible]

[illegible] emias of pregnancy," completely lacks support since no one has ever found the alleged toxin or produced more than presumptive evidence of its existence. The pathologic findings, though characteristic in kidney and liver, are not such as can be demonstrated in eclampsia alone. Josephy and Hirsch (1946) reported that the brain of a woman who had survived eclampsia for three [illegible]

[illegible] man (1943) had reported a similar case, the patient having survived seven years Many theories of etiology are current, some quite interesting, some hopelessly weak, all inconclusive Perhaps the "explanation" that is currently attracting most interest is that symptoms result from the inadequate destruction of the naturally produced postpituitary pressor principles in the liver, plus the deficiency of acetylcholine in the placenta and the blood. Hofbauer (1946) recently reviewed this viewpoint, but I should like to point out that the findings of Krieger and Kilvington (1946) did not support the claim that antidiuretic hormone is a factor in the causation of eclampsia. However, be the etiology what it may, certain gross facts are crystallizing in clinical consciousness. One is that there are definitely two stages in the malady—preeclampsia and eclampsia—that differ in degree only Another is that the serious symptoms are those of water retention And another that if this retention is recognized early enough, much can be done to prevent its progression to the point at which life is threatened. Fortunately no intricate or protracted laboratory studies are necessary, for the diagnosis can be simply arrived at. Headache of sudden onset, visual disturbances, eyeground abnormalities, diminished urinary output, patent edema, nervous irritability—these are helpful but often late manifestations, excessive increase in weight, rise in blood pressure, albuminuria are the cardinal signs to seek and heed. They may appear and disappear independently of one another, but the presence of any one of them is warrant for action. Women do not normally [illegible]

[illegible] and passes from a rigid spasm with opisthotonos, flexed arms, clenched fists, distorted features and dilated pupils into a clonic convulsion, during which

the whole body twitches very violently, the tongue is protruded and often severely mutilated by [illegible] the face is swollen anc [illegible] and the pulse is rapid [illegible] thirty seconds to one and one-half or two minutes, relaxation takes place and the patient may wake up very exhausted and bewildered; or in the most severe cases, she remains in coma between spasms and may be delirious.

According to Stander *et al.* (1946), postpartum eclampsia may in rare instances occur at any time during the first week of the puerperium; Winterton (1946), however, reported what seemed to be a well substantiated case occurring on the twenty-sixth day after the delivery.

THERAPY

There are many methods of treating eclampsia; some of them, like the famous Stroganoff and its modifications, consisting in little more than heavy narcotic drugging when the convulsions occur; others, like the Rotunda, and the approach upon the basis of a supposititious hypoglycemia, relying principally upon the free administration of fluids when the convulsions appear; [illegible] roles; and some [illegible]

of these methods here for the reason that it seems to me advisable only to present the more rational one that attempts both to prevent and treat the disturbance by concentrating all attention on combating water retention The foremost advocates and routinizers of this type of treatment are the group at Temple University in Philadelphia, where the methods were developed under the guidance of Arnold some years ago. The most recent report of a large-scale application of the "Temple treatment" that I have seen is that of Loughran (1946), who reported that the employment of this regimen in 325 pregnant women in private practice has been associated with a remarkably reduced length of labor, a markedly lessened incidence of dystocia, and the total absence of any real toxic state except in one case of [illegible]

very definite amount of exercise is included, and the [illegible] maintained.

Treatment of the Potentially Abnormal.—This is the group of patients who are apparently well but who have a history of definite or probable *kidney*-impairing disease or of previous pregnancy complications possibly involving the kidneys, as well as all with evidences of latent organic disease, especially of the kidneys

(a) Place on a fluid balance basis at earliest recognition of pregnancy: 30 to 40 ounces (900-1200 cc.) of fluid intake and output daily.

(b) Five small meals daily with no food or drink except at these three-hour intervals

(c) The diet should be very low in salt and sweets, the former increasing retention and the latter increasing thirst. Since Strauss (1939) found hypoproteinemia often present in the last trimester of pregnancy, and Rinehart [illegible] its degree to be greater in preeclamptic than in normal women,

the protein allowance should be higher than ordinarily taken, for hypoproteinemia is in itself conducive to water retention. Indeed Luikart (1946) seems very definitely to have shown in a very large series of patients that those on high protein diets have considerably less tendency to develop eclampsia.

Treatment of the Moderately Preeclamptic.—Patients who have some un- [illegible]

(a) Drastically restrict fluids, or withhold altogether if it seems advisable, until twenty-four hour urine output is known; then chart accurately the intake and output daily, or at intervals of a few days, as the case warrants.

(b) Dehydrate more or less moderately with a few daily, or every other day, courses of magnesium sulfate by mouth: 1 or 2 ounces (30–60 cc) of the saturated solution every hour or two until watery stools are produced.

(c) Meals and dietary ingredients as in (b) and (c) under Treatment of the Potentially Abnormal above, except for the withholding of fluids.

(d) When sufficient dehydration is accomplished, as indicated by reduction in weight and blood pressure, endeavor to maintain water balance as in the preceding potentially abnormal group.

Treatment of the Dangerously Preeclamptic.—Those in whom there is already the threat of convulsive seizures: scanty urine, overweight, edema, alarming hypertension (50–100 points), urinary pathology; subjective symptoms—headache, visual disturbances, mental dulness, "indigestion"—often, but still not invariably, present. The treatment here may necessarily include the following:

(a) If the subjective symptoms indicate great urgency, drain the spinal canal of 40 to 80 cc of fluid, or, if this is impracticable, withdraw 20 to 30 ounces (600–900 cc) of blood by venesection

(b) If the case is less urgent, or after one of the above measures has been [illegible]

the blood stream, magnesium sulfate purging must be employed to get rid of the water through the bowel

[illegible]

reduction, indicate effective dehydration.

(e) In most instances food and restricted fluid intake may be allowed after twenty-four hours if the patient *asks* for it, but often it is necessary to withhold both for thirty-six to forty-eight hours

Treatment of the Convulsive Group.—Patients who, antepartum or postpartum, have reached the convulsive stage or in whom there are signs of impending death without convulsions:

[illegible]

the whole body twitches very violently, the tongue is protruded and often severely mutilated by the champing jaws, the eyes are bulging and bloodshot, the face is swollen and cyanosed, blood-tinged foam comes from the mouth, and the pulse is rapid and pounding. The chest is rigidly fixed. After from thirty seconds to one and one-half or two minutes, relaxation takes place and the patient may wake up very exhausted and bewildered; or in the most severe cases, she remains in coma between spasms and may be delirious.

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There are many methods of treating eclampsia; some of them, like the famous Stroganoff and its modifications, consisting in little more than heavy narcotic drugging when the convulsions occur; others, like the Rotunda, and the approach upon the basis of a supposititious hypoglycemia, relying principally upon the free administration of fluids when the convulsions appear; others using bizarre drugs in allegedly more or less "specific" roles; and some [illegible]

present the more rational one that attempts both to prevent and treat the disturbance by concentrating all attention on combating water retention. The foremost advocates and routinizers of this type of treatment are the group at Temple University in Philadelphia, where the methods were developed under the guidance of Arnold some years ago. The most recent report of a large-scale application of the "Temple treatment" that I have seen is that of Loughran (1946), who reported that the employment of this regimen in 325 pregnant women in private practice has been associated with a remarkably reduced length of labor, a markedly lessened incidence of dystocia, and the total absence of any real toxic state except in one case of chronic nephritis (which Loughran, and probably everyone else, does not believe is in any way influenced by this type of regimen) Loughran believes that these results can be reproduced at will in a patient who is willing to cooperate if the high protein, high vitamin and low carbohydrate diet is instituted, a very definite amount of exercise is included, and the fluid balance is properly maintained.

Treatment of the Potentially Abnormal.—This is the group of patients who are apparently well but who have a history of definite or probable kidney-impairing disease or of previous pregnancy complications possibly involving the kidneys, as well as all with evidences of latent organic disease, especially of the kidneys.

(a) Place on a fluid balance basis at earliest recognition of pregnancy: 30 to 40 ounces (900-1200 cc.) of fluid intake and output daily.

(b) Five small meals daily with no food or drink except at these three-hour intervals.

(c) The diet should be very low in salt and sweets, the former increasing retention and the latter increasing thirst. Since Strauss (1939) found hypoproteinemia often present in the last trimester of pregnancy, and Rinehart (1945) observed its degree to be greater in preeclamptic than in normal women,

the protein allowance should be higher than ordinarily taken, for hypoproteinemia is in itself conducive to water retention. Indeed Luikart (1940) seems very definitely to have shown in a very large series of patients that those on high protein diets have considerably less tendency to develop eclampsia.

Treatment of the Moderately Preeclamptic.—Patients who have some undoubted, even though moderate, indications of approaching danger: overweight, slight or marked edema, hypertension of 30 to 50 points; subjective symptoms still absent or only mild or variable.

(a) Drastically restrict fluids, or withhold altogether if it seems advisable, until twenty-four hour urine output is known; then chart accurately the intake and output daily, or at intervals of a few days, as the case warrants.

(b) Dehydrate more or less moderately with a few daily, or every other day, courses of magnesium sulfate by mouth: 1 or 2 ounces (30–60 cc.) of the *saturated solution every hour or two until watery stools are produced.*

(c) Meals and dietary ingredients as in (b) and (c) under Treatment of the Potentially Abnormal above, except for the withholding of fluids

(d) When sufficient dehydration is accomplished, as indicated by reduction in weight and blood pressure, endeavor to maintain water balance as in the preceding potentially abnormal group.

Treatment of the Dangerously Preeclamptic.—Those in whom there is already the threat of convulsive seizures: scanty urine, overweight, edema, alarming hypertension (50–100 points), urinary pathology; subjective symptoms—headache, visual disturbances, mental dulness, "indigestion"—often, but still not invariably, present The treatment here may necessarily include the following·

(a) If the subjective symptoms indicate great urgency, drain the spinal *canal of 40 to 80 cc of fluid, or, if this is impracticable, withdraw 20 to 30* ounces (600–900 cc.) of blood by venesection.

(b) If the case is less urgent, or after one of the above measures has been taken, give 50 cc. of 50 per cent dextrose solution at four- to six-hour intervals, alternating two or three times in the intervals with 20 cc. of 10 per cent magnesium sulfate solution

(c) The above injections being designed to draw water out of the tissues into the blood stream, magnesium sulfate purging must be employed to get rid of the water through the bowel

(d) If marked improvement is not seen in twelve to twenty-four hours repeat the spinal drainage, or repeat it in four to six hours if symptoms continue urgent. Withhold fluid until output from bowel and kidneys, and weight reduction, indicate effective dehydration.

(e) In *most instances food and restricted fluid intake may be allowed after* twenty-four hours if the patient *asks* for it, but often it is necessary to withhold both for thirty-six to forty-eight hours.

Treatment of the Convulsive Group.—Patients who, antepartum or postpartum, have reached the convulsive stage or in whom there are signs of impending death without convulsions:

(a) Treat as above in all particulars except that the spinal drainage should be repeated at three- to six-hour intervals, and that an opiate or a barbiturate may be given to facilitate the first one if absolutely necessary. The number of drainages will depend upon their effectiveness in stopping the convulsions, restoring consciousness and promoting mental clearing. Venesection is rarely

necessary in addition. Keep the patient warm but seek to avoid the use of hot packs.

(b) Arnold says that though some mortality is inevitable in this group, one may expect to keep it within 5 per cent. As to emptying the uterus, he says that by this planned cerebral dehydration they are enabled to "relieve the patient's head rather than her uterus."

HYPEREMESIS GRAVIDARUM

(Pernicious Vomiting of Pregnancy)

Ordinary "morning sickness" occurs in about 50 per cent of pregnant women, but the severe form with which we are here concerned is rare. It usually begins between the third and sixth week and lasts several weeks to months; the course may be continuous or intermittent. The symptoms are loss of appetite, nausea, persistent vomiting, foul breath, emaciation, intolerable thirst, mental aberration, headache, delirium, ketonuria, coma and death. The pathologic findings in the urine and blood are apparently entirely the result of starvation, dehydration and the loss of chlorides through vomiting. Many patients recover spontaneously, either quickly or slowly, but a few go on to death; before this final event miscarriage usually occurs and the stomach [illegible]

in severe carbohydrate deficiency is at present serving very well as a point for therapeutic departure. Ideas regarding vitamin and endocrine deficiencies have gained some recent support. One observer is convinced that the trouble is due to the patient's allergic reaction to the secretion of her own corpus luteum; another has acted upon the assumption that there is hypersensitivity to all the tissues of the husband. The older classification of cases into neurotic, toxic and reflex types is no longer subscribed to by many observers.

THERAPY

Abortion.—Therapeutic abortion will cure all cases if the mother is not already too near death from starvation and exhaustion to stand the operation. But of course this is not advocated as a routine measure by anyone; indeed, when to empty the uterus is an obstetrical point of such nicety that its discussion has no place in a book of this sort. Certainly, under the newer treatment, this radical procedure is being resorted to much less frequently than was formerly the case.

Psychotherapy.—The nervous element must not be overlooked. Sometimes the severe symptoms will almost miraculously vanish when an obnoxious person, not infrequently the husband, is entirely banished from the presence of the patient; or she will suddenly recover when threats to employ the actual cautery or some other severe form of therapy are seriously made. A few observers believe that there is a psychopathic factor underlying all cases; Hurst, of England, even went so far as to say that the artificial termination of pregnancy cures merely by suggestion, since the patient naturally expects to re-

cover when what she regards as the cause of her vomiting is taken away. Kroger and DeLee (1946) reported the complete relief through hypnosis of nineteen recalcitrant cases.

Carbohydrate Dietary.—The theory of carbohydrate deficiency or glycogen deficiency of the liver as the etiologic factor in the nausea and vomiting of pregnancy was extensively developed independently by Titus and Harding

follows: 1½ ounces of lactose and 2½ teaspoonfuls of sodium bicarbonate dissolved in 1 pint of water, this being approximately 10 per cent of lactose and 2 per cent of soda in solution. Two ounces of this is to be taken every two hours

Dextrose and Saline Intravenously.—In severe cases the patient is hospitalized if possible and given sedatives by rectum and dextrose intravenously.

replenished; many men give the dextrose in saline solution; it is the consensus that insulin administration is not necessary.

Duodenal Tube Feeding.—It is the belief of some men that the liver is gravely disordered in this malady and that additional calories should be introduced through the duodenal tube. The method is to give 3 ounces (90 cc.) of skimmed milk and the same quantity of 10 per cent dextrose solution every two hours throughout the twenty-four; this gives the patient 780 additional calories as well as 2000 cc. more water (see also below).

Vitamin Therapy.—Of course vitamin B complex and its individual con-

valueless. Hart *et al.* (1944) found thiamine hydrochloride and pyridoxine

ever, it might perhaps be the part of wisdom in all severe cases to administer ascorbic acid parenterally and as soon as progress permits add large amounts of vitamins A and D by mouth.

Adrenal Cortex.—Hart *et al.* (1944) gave 2 cc. of adrenal cortex extract for a few days to five patients in whom vitamin treatment had failed, three of the patients were able to retain food when so treated. Several earlier observers had also used this preparation with good effect in some of their cases.

Sex Hormones.—Good results have been reported to follow the administration of progestin, estrogens and testosterone, but the rationale of the employment of none of these agents has been established, of course.

Forced Hydration.—Eller and Randall (1945), assuming that the nausea of

treated their patients by forced hydration, i e., they were required to take four

gurgle of the flushing toilet would have relieved them of their husbands as well. Furthermore, can it be a wise thing to force the ingestion of large quantities of water upon pregnant women?

Husband's Blood.—The patient of Hughes and Martin always awakened after intercourse with a headache similar to that which she experienced eating certain foods to which she was sensitive; when she developed hyperemesis gravidarum it was felt that possibly the developing tissues of the fetus following the husband's characteristics also might be incompatible with the mother and that the severe hyperemesis was a response to this tissue incompatibility. *Intramuscular injections of the husband's blood were therefore given in the* hope that they would stimulate the formation of products that would counteract this tissue sensitivity. The patient had been pregnant on seven preceding occasions, having experienced severe vomiting and spontaneous miscarriage

week

as in-

jected intramuscularly every three to eight days throughout the entire pregnancy, the longest interval being two weeks. Great relief was afforded by these injections and the pregnancy went through uneventfully until the 36th week when it was thought advisable to induce labor because of threatened toxemia. Upon one occasion the patient's own blood had been substituted for that of the husband without effect. This is only one case report which may

GENITO-URINARY INFECTIONS AND STONE

GONORRHEA

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to prevent free voiding, but infiltration of the corpus spongiosum is sometimes sufficient in degree to destroy the elasticity of the urethra so that on erection the penis curves downward, giving rise to the very painful symptom known as chordee. When the infection spreads behind the sphincter, which occurs in the majority of cases between the second and fourth weeks, the so-called "posterior" urethritis is established, in its train often come prostatitis, epididymitis and seminal vesiculitis Gonorrhea in women may be indicated in the

old, when the cornified layer of epithelium has not yet formed or has disappeared,

vaginal orifice may become hot and rough and tender but they are not in themselves infected by the gonococcus in the beginning, indeed many infected women are unaware of the fact Pelouze (1946) said it was the consensus of those who studied many of the promiscuous young girls accused of infecting our military personnel during War II that about 90 per cent had no symptoms or any mucosal blemishes to suggest that gonococci were present. However, though the discomfort of acute gonorrhea in women usually passes away very quickly, the process nearly always becomes chronic, as in the male. The natural barriers against the upward extension of the infection into the uterus and the adnexa are very great, but once this extension takes place the resultant endometritis, salpingitis, and so on, are serious affairs indeed Noeggerath, in 1872, was probably the first to lay stress upon the importance of latent gonorrhea in the female

Gonorrhea is believed to outrank in incidence a number of the common infectious diseases in children, but its true incidence is unknown. Its greatest frequency is in girls up to the age of five years, but it may occur at any age up to puberty. The disease is contracted indirectly from infected adults,

so frequently involved that the disease would more aptly be styled "cervico-vaginitis." The symptoms are painful urination and pain on walking, pronounced redness and edema of the external genitalia, coapted labia majora and a thin watery secretion which soon develops into a thick, yellow, offensive discharge. The gonococcus can be demonstrated in about 50 per cent of cases; rectal cultures are also often positive but clinical proctitis seems to be very rare. In the majority of instances the condition undergoes spontaneous cure in about three months, but in many children the infection causes considerable discomfort and lasts as long as six months, occasionally for several years. The impression that the disease terminates invariably at puberty is a common one, but Benson and Steer (1937) recorded two girls in their clinic still showing positive smears though menstruating six and eight months respectively at the time of report. Complications are fortunately very rare in these cases in childhood, though Maguire (1944) stated the belief that gonorrheal pelvic inflammatory disease occurs sufficiently often in young children to be considered in the differential diagnosis of acute abdominal pain in these patients.

Gonorrheal arthritis, first clearly described by Brande in 1854, and endocarditis are serious complications, which occur of course only after the organism has entered the blood stream in considerable numbers. Keratoderma blennorrhagicum (gonorrheal dermatitis) is a rare complication of gonorrhea in the skin that may occur unassociated with urethritis. If the gonococcus is conveyed to the conjunctiva by the hands or other contaminated object an acute infection often resulting in blindness follows, that this catastrophe does not occur with greater frequency than is the case is solely due to the fortunate fact that the organism perishes very quickly outside the body, though cases of its survival on damp towels for twenty-four and dry towels for twelve hours are on record (Dobszay, 1933) In most cases of gonorrhea there are few [illegible]

[illegible] tient's fear that what he looks upon as his moral dereliction will be discovered.

Gonorrhea would seem to be as old as man, for very many of the ancient writings that have come down to us, both religious and secular, contain references to this "flow of semen" disease. However, so far as we now know, the true nature of the discharge and the recognition of the infectious and venereal [illegible]

[illegible] Hunter's day (1728–1793) we find the two diseases again confused, [illegible] 1838, finally established the separate entities. In 1879, Neisser discovered the causative organism, now known as *Neisseria gonorrheae*. Regarding the present incidence of the disease, it can only be said that it is very prevalent all over the world, but whether it is on the increase or decrease cannot be stated with any positiveness, though the draftee rejections in War II as compared with War I indicated that the incidence has declined in the United States.

THERAPY

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men Nothing would be gained by analyzing here the many large series of cases that have been reported, for the facts are now common knowledge.

Romansky Formula Intramuscularly.—Heller (1946), Chief of the Venereal Disease Division of the United States Public Health Service, reviewing the results obtained with penicillin in that Service, reported on two treatment schedules: one that could be completed in two hours and another that required three hours. There were 396 patients studied, 248 white and 148 colored, 108 male and 288 female, the diagnosis being made by culture in all patients. To be considered "cured" in this series the patient had to be clinically and bacteriologically free of the infection, *i.e.*, without signs or symptoms and with three or more cultures all negative during the observation period (six to nine days in 17 per cent of the cases, ten days or longer in 83 per cent of the cases). In the two-hour schedule the patients received 200,000 units of penicillin dissolved in 6 cc of water in three intramuscular injections: at 0 hour, 50,000 units (1.5 cc.), at 1 hour 50,000 units (1.5 cc.) and at two hours 100,000 units (3 cc). The three-hour schedule consisted in the use of 40,000 units at 0 hour and at 1 hour and at 2 hours, and at 3 hours a final injection of 80,000 units. Among the patients observed ten days or longer, 94 per cent were cured on the two-hour schedule and 96 per cent on the three-hour schedule. These results approximated those previously reported by Van Slyke and Heller (1945) on 1060 cases treated by private physicians, clinics and rapid treatment centers with a single intramuscular injection of 200,000 units in peanut oil and beeswax, in that in this latter study 92 2 per cent of the cases were classified as cured. It therefore seemed from a comparison of these two studies that the single injection of the penicillin in beeswax and peanut oil was just as good as the multiple injection method. It is to be noted that this beeswax-peanut oil mixture is less potent than the Romansky formula of 300,000 units of penicillin in peanut oil and 4.8 per cent beeswax; this latter preparation is the one now almost universally employed.

Penicillin by Mouth.—It seems that the practicability of employing penicillin orally in the treatment of gonorrhea has been demonstrated. Bushby and Harkness (1946) treated sixty-two cases for fifteen hours with 240,000 units (40,000 at three-hourly intervals), only two of the cases failing to be cured on this first course, a cure rate comparing very favorably with that achieved by parenteral administration. However, these observers warned of the importance of regular dosage and of restricting the fluid intake during the period of the treatment to one and one-half pints. Cohn *et al.* (1946) compared several methods of oral administration in a total series of 111 patients and found the best results were achieved when the patient was given 24 pills each containing 25,000 units of penicillin and was instructed to *swallow six pills (150,000 units) at once, to be followed by two pills (50,000* units) every hour for the following six hours; on the seventh hour he was instructed to take the remaining six pills (150,000 units). With this method a cure rate of 92 per cent was achieved in the fifty patients (forty men and ten women) in which it was used Bohls *et al.* (1946) obtained a cure rate of 97.2 per cent in thirty-six female patients to whom they gave 200,000 units at 8 A.M and again at 4 P.M., using a tablet containing 25,000 units of penicillin with aluminum potassium sulfate and sodium benzoate.

Results in Genito-urinary Complications.—In the large series of cases of Lees (1946) it was found that the genito-urinary complications of gonorrhea in the male, such as epididymitis, responded rapidly to and were completely

cured by penicillin; this is the universal experience. Gray (1945) reported the successful treatment of thirteen women with verified acute gonococcal pelvic inflammatory disease, giving intramuscular injections of 20,000 to 25,000 units every three hours with usual total doses of 400,000 units. It was said that the symptoms of acute salpingitis and peritonitis showed little or no improvement in twenty-four hours but improved remarkably in forty-eight hours. Cervical discharge changed from the profuse yellow character after three to six days to a white and mucoid type, decreasing thereafter. The inflammation of acute salpingitis usually progressed for seven to ten days after the patients were apparently free of the gonococcus. Tubo-ovarian inflammatory masses and pelvic induration frequently appeared or progressed but subsequently there was improvement and regression. Residual damage was found in all the cases in the series in the form of adherent ovaries or chronic tubo-ovarian inflammatory masses, such damage resulting whether or not palpable masses and induration had been present before the institution of treatment.

Results in Vulvovaginitis.—Lee and Sussman (1946) reported the successful treatment of thirteen cases, ten of which were acute and had had no previous therapy and three of which had been treated with sulfonamides without cure; all of these cases were quickly cured with penicillin no matter how administered. Eight of the girls received 100,000 units divided into six or seven equal doses given intramuscularly at two-hour intervals, one girl the same amount divided into eight equal doses at two-hour intervals, one girl a single intramuscular injection of 150,000 units in beeswax-peanut oil and another a first dose of 150,000 units in the beeswax-peanut oil and a second five days later of 300,000 units in the wax and oil, one girl received 20,000 units every four hours for six doses orally, one girl 25,000 units every two hours for twelve doses orally, one girl 50,000 units every four hours for six doses orally.

Results in Ophthalmia.—Sorsby (1945), as the result of experience in the treatment of sixty cases of gonorrheal ophthalmia, evolved the following five stage treatment: (1) On admission, after swabbing for smear and culture, irrigate with half-normal saline at room temperature, instill a drop of 1:1000 epinephrine solution, and take a scraping from the palpebral conjunctiva to be examined for the presence of inclusion bodies; a drop of 1 per cent atropine sulfate solution is instilled if the cornea is involved. (2) Wipe away pus with moist pledgets of cotton and instill 1 drop of penicillin in a concentration of 2500 units per cc. (3) Continue the penicillin instillations every five minutes until there is no discharge, irrigation not being needed since pus does not form to any extent. Generally half an hour to three hours treatment (six to thirty applications) is necessary before the eyes dry, and of course this part of the treatment requires the full-time attention of a nurse. (4) When there is no [illegible]

cure.

Results in Keratosis.—Freireich *et al.* (1947) reported the successful employment of penicillin systemically in two of three cases of keratosis blennorrhagica.

Results in Endocarditis.—Myers (1947) reported the cure of a case of prob-

able acute gonococcic endocarditis of the pulmonary valves and stated that the cure or clinical arrest of three of five other such cases had been reported to him by Keefer; this is an amazing thing because in the pre-sulfonamide and pre-penicillin days the mortality in this infection was practically 100 per cent.

Results in Arthritis.—Hench (1946), in attempting to explain why penicillin cures only about 58 per cent of cases of gonorrheal arthritis, advanced the following possible reasons: (a) inadequate dosage; (b) possible relative impermeability of the synovial membrane to penicillin, given parenterally; (c) the possibility that penicillin-resistant strains of gonococci are being encountered,

for inadequate penicillin dosage; as a matter of fact we know that penicillin does penetrate rapidly into synovial fluid when given parenterally and attains therein levels comparable with those in the blood serum, and even if it did not its failure to do so would probably not be of importance because, as pointed

course tardiness in initiating treatment can easily allow such an amount of irreparable articular destruction to occur that complete functional recovery

G (the most potent penicillin) and more K than before or since Hench's opinion is that the most common cause of past and future failures in the treat-

gonorrheal arthritis at all but were cases of rheumatoid arthritis in men who happened to have gonorrhea or of rheumatoid arthritis precipitated, reacti-

gonococci that remained persistently resistant to penicillin However, Franks (1946) reported four cases in which the organisms were found to be penicillin-resistant *in vitro* and in which combined sulfonamide-penicillin and fever treatment was employed with good success. Naturally, therefore, Franks is

gonorrhea, it was the opinion of these observers that clinical and serologic

observation for ninety days from the date of treatment may be expected to suffice to detect all but the most exceptional cases of syphilis. It seems that such a three-month period of observation is the aim of the present policy of the United States Army, and Heller (1946), of the United States Public Health Service, has made a strong plea for the private physician treating gonorrhea to include along with the physical examinations a serologic blood test for syphilis at the beginning of treatment and at the end of the first, second and third months whenever possible.

Streptomycin.—In order to determine whether we might have another string to our bow in the event that penicillin, now undisputed champion in the treatment of gonorrhea, should eventually fail us, Chinn *et al.* (1947) tried streptomycin in four men with acute gonorrhea confirmed by smear and culture, giving each 0.1 gm. of streptomycin sulfate dissolved in 3 cc. of physiologic salt solution at hourly intervals for five doses. All these patients were observed daily for three days post-treatment and at the seventh and tenth days, three consecutive negative cultures within ten days after therapy in the absence of a marked improvement in clinical findings being considered evidence of cure. All four of the patients responded promptly within twenty-four to forty-eight hours by a reduction or cessation of the urethral discharge

in aqueous solution as a single injection intramuscularly. Fifty patients were given 0.3 gm. or more (fifteen received 0.3 gm., ten 0.4 gm., and twenty-five 0.5 gm.); 100 per cent of cures was achieved in these cases.

Sulfonamides.—At the time of the appearance of the last edition of this book, there was reason to believe that the sulfonamides were about to lose their high position in the treatment of gonorrhea for the reason that a very considerable amount of sulfonamide resistance was found among patients the Armed Forces during War II. And as time has passed the proportion of cases not responding to these drugs has progressively increased. It seems now that some strains of the gonococcus are completely unaffected by the drug ... and that others acquire resistance quite easily. ..., since at the present time we find ... the gonococcus here in the United States, is that the most sensitive strains seem to have been killed off and the resistant strains alone have survived and continue to propagate the disease. I shall not devote space in this present edition of the book to a description of the methods of employing these currently unsatisfactory agents.

Last Resort Urological Therapy.—In a patient in whom it is not possible to obtain a negative prostatic smear after successive courses of penicillin, the only recourse that can be had is to streptomycin, and if that fails, to fever therapy. All of this failing, I imagine the case should be referred to a urologist, who may possibly resort to catheterization of the ejaculatory ducts and irrigation of the seminal vesicles. ... plications

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and the vigorous blowing of zinc peroxide powder about the glans penis and under the foreskin is a measure that is very helpful in effecting reduction of the swollen prepuce Taylor (1944), on the basis of long experience, advised immediate circumcision as the treatment of choice in cases of phimosis with swelling of the prepuce or ulceration beneath it; at the operation he favors cauterization of the ulcers with pure phenol that is not later neutralized, and possibly the resection of the ulcers. This seems much more radical treatment than would probably be often indicated in cases seen here in this country; Taylor's cases were seen in China where apparently phimosis is very common and penicillin not easily obtainable Of the treatment of paraphimosis, Pelouze (1936) wrote: "The foreskin should be replaced as early as possible to prevent induration and ulceration at the point of greatest constriction. In order to do this the glans penis should be grasped by the gloved fingers of one hand, while the other hand is used to encircle the swollen, misplaced prepuce Gentle, continuous pressure should be made upon both structures until about all of the swelling is gone. The parts then usually are easy to place in their normal positions. To prevent subsequent retraction it is well to pass a strip of adhesive plaster along one side of the penis, over part of the preputial opening in such a way as to make it smaller, but not occlude it, and then down along the other side of the penile shaft. This should be left on for several days In the presence of neglected paraphimosis with much induration it occasionally is necessary to incise the constricting band on the dorsum of the penis. If ulceration has taken place it is wise to attempt to sterilize the surface by the application of tincture of iodine before incision of the constriction. Ulcerations of the glans penis from prolonged penile constriction usually heal promptly upon the use of an antiseptic dusting powder. Before this is used, however, a darkfield study of the ulcer fluid should be carried out."

SYPHILIS

(See under *Infectious Diseases*)

CHANCROID

Chancroid is, next to gonorrhea, probably the commonest of the venereal diseases in the male. The finding of ulcers in 53.3 per cent of sixty cases in women, studied in Manila by Lao and Trussell (1947), is certainly a much higher incidence than is usually reported in that sex, though Allison (1945)

the genitalia. The bacillus of Ducrey is the causative agent but is very difficult to find Strakosch *et al* (1945) obtained positive cultures in 219 of 370 cases, but positive smears in only 159 Of the 370 patients, 256 had a positive, thirty-six a doubtful, and fifty-three a negative Ito-Reenstierna intradermal test. Of the 163 patients in the series with chancroidal lesions but no evidence

or history of syphilis, twenty-one gave a *positive* Kahn *reaction*, the titer declining and eventually becoming negative with the clinical improvement of the lesion. Heyman *et al.* (1945), in the study of 125 cases, found biopsy the

Perhaps one will be hearing again of the employment of auto-inoculation as a diagnostic method now that the sulfonamides have made it completely safe. The incubation period is usually considered to be three to five days but occasionally it is as short as one day; in Satulsky's (1945) series of 1555 cases

by contiguity and continuity, discharging more or less pus, bleeding freely and causing destruction of tissue. The most frequent site of the initial lesion is the coronary sulcus, but the process may begin at any point on the penis; extragenital lesions are extremely rare, but spread by auto-inoculation may take place on the surrounding pubic region or on the abdomen and thighs. Intra-urethral chancroid has been recorded. As the ulcerations spread, there is much pain and inflammation and swelling of the affected parts. In the *individual with a long foreskin there often occur varying stages of phimosis* and paraphimosis. In about 50 per cent of the cases, especially those remaining ambulatory, the draining lymph glands are affected, giving rise to the condition known as bubo.

John Hunter (1728–1793) clearly distinguished between true syphilitic chancre and this false "soft" chancre. Ducrey discovered the causative *Hemophilus ducreyi* in 1889.

THERAPY

Sulfonamides.—Experience in recent years has shown the systemic *employment of sulfonamides to be superior to local treatment* in all stages of the infection—ulcer, bubo ruptured or bubo unruptured. The simple local treatment nowadays employed (see below) is of an entirely new sort. Sulfa-

days; or sulfanilamide was used in dosage of *15 grains (1 gm.) three times a* day for five days followed by 10 grains (0.6 gm.) four times a day for ten days The average hospitalization of all lesions in this series was 11.2 days. In the 350 sulfathiazole treated cases of Harp (1946), healing occurred on the average on the ninth day after sulfathiazole was started; he found the efficacy of this agent more apparent in the treatment of large ulcers measuring more than 10 mm. in diameter.

Penicillin.—This agent has not been very effective in the *treatment of* chancroid. Indeed in Pereyra and Landy's (1944) study in patients experimentally inoculated, it seems that the intramuscular injection of penicillin *actually facilitated the development of a chancroidal lesion.* Twenty-five of the patients of Strakosch *et al.* (1945), who were treated for primary or secondary syphilis with penicillin, had a chancroidal infection at the same *time;* the dosage of penicillin employed at that time was only 300,000 to 600,000

units in seven and a half days, and it was noted that if the chancroidal lesions were small they healed but that otherwise sulfathiazole therapy was necessary. Sulzberger (1945) has very cogently remarked that he thinks it rather fortunate that penicillin is not particularly effective in chancroid cases, for if the lesion responds to sulfonamides it means we have been dealing with chancroid rather than chancre.

Local Treatment.—The accessible lesions are cleansed with soap and water, dried, and covered with sulfanilamide or sulfathiazole powder or sulfathiazole ointment. This treatment is repeated daily by those who employ it but as a matter of fact many men no longer find it of advantage to use the sulfonamide locally when it is being given systemically. The treatment of phimosis and paraphimosis is discussed in Gonorrhea

Bubo.—Greenblatt (1943) stated authoritatively that the bubo should never be incised. If fluctuation is present the bubo may be aspirated with aseptic [illegible]

be [illegible]
of [illegible]
b [illegible]
tr [illegible]
bandage was applied and the patient kept at bed rest for three or four days, during which time there was drainage of an iodine-stained semipurulent serum and clumps of purulent material, in five to seven days the area was completely healed without any sequelae.

BALANITIS

Erosive balanitis is an infectious venereal disease due to the symbiosis of a fusiform bacillus and a spirochete, both of which are anaerobic and structurally resemble those found in Vincent's angina It is a fairly uncommon affection even in large venereal clinics Red superficial lesions with a necrotic border appear on the glans or foreskin and enlarge peripherally and become confluent to form circinate lesions with polycyclic borders. They do not give rise to bubo [illegible]
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plic [illegible]
gang [illegible]
and prepuce, and in some instances the entire shaft of the penis, being destroyed in a surprisingly short time. In this gangrenous form of the disease there are always grave constitutional symptoms and death is frequent.

THERAPY

Penicillin Therapy.—In seven cases, Cutler, *et al.* (1947) instilled 1 cc of penicillin diluted to contain 20,000 units per cc. into the preputial sac, the solution being maintained in place for about fifteen minutes and then discarded, the process being carried out only once. It was said that within fifteen to thirty minutes after completion of therapy there was noted a decline in severity of the pain, and that within twenty-four hours there was complete

relief of pain and no motile spirochetes could be found. The secretion was diminished and no longer foul-smelling, the edema had begun to subside

was complete, the edema had subsided and the glans was found to be dry.

completely uncovered, and then to keep the parts clean either by wet dressings or by continuous irrigation with 2 per cent solution of hydrogen peroxide. Most cases of the erosive type heal rapidly under this treatment, especially if the parts are kept exposed to air at all times when the oxidizing agent is not being used. Sutton has described the use of subcutaneous injections of oxygen in a case of the gangrenous type as follows: "When I first saw the patient, five days after the onset of the disease, almost the entire dorsum of the penis was involved, the skin and subcutaneous tissues being soft and gangrenous. During the following thirty-six hours the infection continued to spread, *despite the frequent and liberal use of hydrogen peroxide, by irrigation and by* moist packs. At this time subcutaneous injections of oxygen were begun, by means of an ordinary hypodermic needle connected to an oxygen tank through a small rubber tube, and repeated every four hours. The normal tissue surrounding the affected area was first treated, the flow of gas being regulated by means of a small screw clamp encircling the outlet tube. Afterward the involved structures also were thoroughly impregnated with the gas. Within six hours the progress of the disease was checked, and within twelve hours it was completely under control. Shortly afterward the slough began to separate, and recovery, aside from the deformity resulting from loss of tissue, was prompt *and uneventful.*" *Balanitis being an uncommonly encountered disease,* it is not probable that this type of treatment has been much employed; indeed, I have neither seen nor heard mention of its use other than in this one case of Sutton's.

GRANULOMA INGUINALE

(Granuloma Venereum)

Granuloma inguinale is a chronic infectious, ulcerative process, usually involving the genitalia or neighboring parts, and showing no tendency toward spontaneous healing. Most of the cases are seen in young adults with perhaps an even distribution between the sexes. Here in the United States it is predominantly a disease of Negroes, and in India the preponderance of Hindu over Mohammedan cases is said to be very high; I do not know to what extent the matter of racial preference has been investigated in other parts of the

of transmission during coitus by means of infected pubic lice. The p-
begins as a small moist papule that rapidly ulcerates; thereafter, invasion of the surrounding tissues by the elevated, reddish, often shiny, delicately skinned granulomatous proliferations is gradual and eccentric. Where moist, the lesions are superficially ulcerated, but where dry they are cracked. Adenopathy is

characteristically absent except in rarest instances, though the occurrence of elephantiasis of the genitalia, or of a leg, signifies involvement of the lymph channels Except for the presence of the lesions and a slight itching or burning sensation, the patients experience little discomfort The discharge from the ulcerating areas is held by some observers to have a quite characteristic odor, but having once seen the entire staff of a reputable hospital led temporarily away from their correct clinical diagnosis of epithelioma by the asseveration of an expert in this disease that he "smelled granuloma in the ward" I am extremely doubtful of the value of this diagnostic sign. Anderson *et al* (1945) are attempting to standardize a diagnostic skin test employing antigens obtained from the organism they have described. In many case reports in recent years there has been accumulating evidence that granuloma inguinale is a general systemic disease that may involve bones, joints, soft tissues and internal organs, and that it can terminate fatally.

The disease was recognized by MacLeod, in India, in 1882, but it was first accurately described by Conyers and Daniels, in British Guiana in 1896. In 1905, Donovan, in India, first described the organism now believed to be causative, but strange to say it is not definitely known as yet whether this organism is a protozoan or a true bacterium. The Donovan body is found in all parts of the lesions, but especially in the deeper areas, where all other organisms are absent. The characteristic histologic picture described by Pund and Greenblatt in 1937 now seems to be recognized by other workers as well; Alexander and Schoch (1940) found the use of Giemsa stain necessary to bring out the pathognomonic giant-cell Increasing knowledge indicates that the disease is practically world-wide in its distribution; here in the United States it is undoubtedly more prevalent in the South than elsewhere.

THERAPY

Streptomycin.—The preliminary study of Greenblatt *et al.* (1947) in twenty-three patients indicated that perhaps, both on the basis of clinical improvement and the rapid disappearance of the Donovan bodies from smears, this will be found the most effective agent available for the treatment of granuloma inguinale The daily dosage in this study ranged from 0 3 to 1 gm. per twenty-four hours, divided into equal amounts at four-hour intervals; the period of administration extended from six to forty-six days. Daily smears from the lesions failed to yield Donovan bodies after five to nine days' Healing followed a general and usually centrifugal pattern but was slowest where moist ulcerated areas were in constant contact with one another.

Antimony.—Antimony has had a long trial but its record is certainly not brilliant; the newer compounds are considered to be less toxic than tartar emetic itself. Antimony toxicity is discussed in Leishmaniasis

Tartar Emetic.—Antimony and potassium tartrate was first used in the treatment of this disease by Aragão and Vianna of Brazil. In cases responding satisfactorily the lesions involute progressively and the Donovan bodies disappear. It is customary to use a 1 per cent solution beginning with 2 cc. intravenously and increasing 1 to 2 cc. at a time until 10 to 12 cc. are being given at a dose. The injections are given at intervals of two to three days.

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(1942) only freshly prepared solutions should be used, the stock solutions in ampules being found by them of little value. It is now the consensus that good results are to be expected only in early cases; Greenblatt (1943) said that cure may be obtained in practically every case where the diagnosis is made within the first six months of the infection, that over 50 per cent of patients with lesions of several years' duration will respond much more slowly and with frequent recurrences, and that in neglected or therapy-resistant patients the lesions will gradually become very extensive and the patient will become bedridden and cachectic and will finally die of the disease. Response to the drug seems to be much less complete when syphilis is present as a complication.

Antimony Sodium Thioglycollate.—The dose of antimony sodium thioglycollate is 0.05 to 0.1 gm. dissolved in 10 to 20 cc. of sterile water and given intravenously every third or fourth day until fifteen to twenty-five injections have been given. This drug was introduced a great many years ago but it does not seem to have been much employed; however, Robinson *et al.* (1942) reported its use in two patients who did not respond to tartar emetic and that in them the lesions healed promptly with six and eight doses respectively.

Fuadin.—The reports on this drug have certainly been conflicting though Greenblatt (1943) felt it to be superior to tartar emetic and more convenient to administer. Berkowitz (1946) also recently reported its satisfactory use. The dosage of the latter observer in his two cases was 1.5 cc. of the ampule solution (6.3 per cent) on the first day, 3.5 cc. on the second day, 5 cc. on the third day, and 5 cc. every third day for six doses, a total of 40 cc. There were no reactions to the drug and no pain resulted from the injections.

Antimony Thioglycollamide.—Hazen (1932) used this agent with "striking therapeutic response" in three cases, Senear and Cornbleet (1932), and Patch and Blew (1930), also used the drug successfully I have seen no recent reports of its performance though it continues to be Council-accepted.

Anthiomaline (Lithium antimony thiomalate).—Greenblatt (1943) seemed to consider the usefulness of this compound about the same as that of fuadin. Robinson *et al.* (1942) used it as the sole drug in four cases and obtained cures in all; in nine tartar emetic-resistant cases satisfactory results were obtained in only two.

Diramin.—Greenblatt *et al* (1945) reported the use of this new compound in fourteen patients. The drug was given intravenously in 2 cc. dosage two to five times weekly, the intramuscular route having proved too painful. It was concluded that diramin is a "good, safe preparation to use" in the treatment of granuloma inguinale.

[illegible] reported rapid healing [illegible]

[illegible] complete than under [illegible]

such as pontocaine, metycaine or nupercaine ointment, ten minutes before [illegible] podophyllin application to prevent the pain of which many patients complain; (c) discontinue podophyllin application when the exuberant granulations have disappeared and a healthy base is evident and then apply scarlet red ointment

after each bath in order to stimulate epithelialization; (d) when necessary

[illegible]

Robinson *et al.* (1942). They employed surgical excision in sixteen cases, in fourteen of which other measures had failed; complete healing followed the operation in nine instances and partial healing in five. Greenblatt (1943) said that if lesions are extensive several courses of radiation therapy should be administered in dosage similar to that employed in the treatment of skin cancer; but in the three cases of Robinson *et al* (1942) such therapy did not bring about involution of the process in any instance.

LYMPHOGRANULOMA VENEREUM

(Lymphogranuloma Inguinale, Climatic Bubo, Venereal Lymphogranuloma, Lymphopathia Venereum)

This is a specific venereal disease contracted almost exclusively through sexual exposure and therefore seen with extreme rarity in children. Men predominate among the victims of the inguinal form, but the anorectal localization is seen often enough in women (occasionally in men also) probably to equalize the sex distribution; elephantiasis of the pudenda is also a manifestation of this disease. The initial small lesion on the external genitalia is not often seen, but it is known that the incubation period after exposure is between three days and three weeks. Usually the glands of only one side are involved but bilateral cases are seen not infrequently, there is gradual progression until a fist-size mass bound together by periadenitis is formed, and then breakdown and fistula formation take place; a thin seropurulent fluid drains for weeks and months. Occasionally, however, no breakdown occurs. Ocular and skin lesions have been described a number of times. The rectal lesions begin with proctitis and a bloody and somewhat purulent discharge, and they usually lead to serious stricture interfering with defecation and complicated by infection of the perirectal as well as the rectal and anal tissues; the most dreaded complication is rectovaginal fistula The studies of Wilson and Hesseltine (1942) and Finn (1944) indicated the possible hazard of mismanaged labor if the pelvis is obstructed. There is some evidence that lymphogranuloma may predispose to the development of neoplastic disease. Constitutional symptoms of varying severity are observed in the majority of cases in the acute stage. Remote lesions suggesting a generalized systemic infection have been described—recent records include Zaraf[illegible] auth[illegible] in v[illegible] lesio[illegible] agent is soon destroyed. That the causative organism is a filtrable virus was shown by Hellerström and Wassén, in 1930; it may be isolated not only from the bubos but also from the blood and spinal fluid, and it is successfully grown on the chick embryo It is interesting that evidence is accumulating of some possible relationship between the agents causing lymphogranuloma,

psittacosis and trachom- [illegible]
1925 has greatly stimu [illegible]
however, that the test [illegible] in some instances in which there are no clinical evidences of infection—indeed, Koteen (1945) said that a positive test indicates only that the patient has at some time been infected with the virus and has no necessary bearing on the nature of the presenting lesion; a repeatedly negative Frei test he felt to be reasonably strong evidence of the absence of lymphogranuloma. In discussing the complement fixation test, which they had thoroughly studied, Wall *et al.* (1947), of Beeson's group, said that the occurrence of cross reactions caused by infection with other agents of the psittacosis lymphogranul [illegible]

[illegible] granuloma in patients with chancroid and other venereal diseases are caused by associated or previous infection with the virus of lymphogranuloma and are not the result of nonspecific reactions. I do not know how many men experienced in this field will accept that viewpoint

It is now thought that John Hunter treated cases of lymphogranuloma inguinale because of some descriptions in his "Treatise on Venereal Diseases," published in 1786, many men later described similar clinical pictures, but the individuality of the disease and its probable venereal nature were only truly pointed out by Durand, Nicolas and Favre, in 1913. Originally considered to be only tropical in its distribution, it is now recognized as occurring practically everywhere, though the greatest incidence seems to be in the warm, humid lands; however, Schutte and Lubitz (1940) found 33 cases in the proctologic clinic of our own school here in Milwaukee.

THERAPY

As in the therapeutic approach to all relatively "new" diseases, a host of remedial agents has been tried: quinine, organic arsenicals, antimonials, sulfonamides, penicillin, diathermy, local application of a filtrate from infected glands, Frei antigen injections, autoserum, x-ray, radium, foreign protein and other fever therapy, surgical extirpation of the glands. Description of the methods of employment of only a few of these seems worthwhile at the present time.

Sulfonamides.—There have been numerous reports of the satisfactory use of the sulfonamides. Heyman *et al.* (1947) reported the recovery of virus from the inguinal lymph nodes in two of three untreated patients for as long as ninety-five days after the onset of the illness, whereas they were unable to recover it after the second and third week in nine patients treated with sulfathiazole. Grace (1943), who has had plenty of experience, categorically stated it as well established fact that sulfathiazole will cause the regression of the adenitis, suppurative and nonsuppurative, within a period of approximately five weeks. He said that cases of short duration without stricture can be completely healed, but long-standing cases, and all with stricture, require at least one year's therapy with rest periods of from two to three weeks after each course of treatment. The amount of anal discharge is said to lessen shortly after treatment is begun and ultimately to cease. Koteen (1945), at Johns Hopkins University Venereal Disease Center, said that it was current practice in that clinic to prescribe 1 gm of sulfathiazole or sulfa-

diazine orally four times daily for two weeks and, if the patient tolerates the drug without reaction, to continue with 3 gm. daily for an additional two or three weeks depending on the involution of the adenopathy. Constitutional symptoms were said to respond within two days and pain to be alleviated, though there might not occur any apparent change in the adenopathy within that time. Koteen felt that it was too early to report on the effect the program would have on the prevention of late manifestations of the disease or its influence on transmission. And he made the rather equivocal statement that the worth of sulfonamides cannot be overestimated, though evaluation of them is not yet complete. One cannot easily overlook Hepburn's (1947) report that twenty-six cases in the stage of inguinal adenitis admitted to the hospital ship *Repose* in Shanghai were found to respond to supportive care, aspiration, and in one case excision, in approximately the same time as sulfonamide-treated cases reported in the literature. Wright *et al* (1946), on the basis of considerable experience at the Harlem Hospital, felt that the sulfonamides in the pre-stricture stage may in some instances prevent further progress of the condition and in this way stop formation of strictures, but since no evidence has been forthcoming that the sulfonamides are virucidal in their action, they were somewhat skeptical of their overall value. It was their opinion that in patients in whom the symptoms and signs are predominantly due to congestion, edema and ulceration caused by secondary infection, the sulfonamides are of positive value, but that since it is obvious that drugs cannot remove scar tissue, these agents do not and cannot cure fibrous stricture of the rectum.

Antimonials.—In 1939, D'Aunoy and von Haam reported that their best success had been with antimonials. Recently anthiomaline (lithium antimony thiomalate) has had considerable trial In the United States, Shaffer (1942) injected it intramuscularly in a dosage of 0.12 to 0.3 gm in aqueous solution, repeating injections two to three times a week in courses of 2 to 4 gm., totaling 12 to 20 injections. It was his conclusion that the drug was not a completely satisfactory preparation for the treatment of all forms of the disease but that [illegible]

though in a few instances he found it necessary to substitute tartar emetic when the newer drug was not available. He found that results were just as favorable with antimony as with sulfonamides.

Grace (1943) stated his feeling that perhaps lymphogranulomatous proctitis should be treated by alternation of a sulfonamide compound and inactivated virus, the latter to be administered intravenously and derived from the infected chick embryo. He thought that the failures in the employment of Frei antigen by earlier observers were due to the low concentration of virus in the human or mouse brain preparations employed.

Autoserum.—Marks (1942) treated fifty patients by reinjection of their own serum. Ten to 15 cc. of blood were removed from the median basilic vein and the serum separated from this was injected under the skin of the abdominal wall. There were no severe local reactions and apparently no systemic ones. Treatments were given at four-day intervals in a course of twelve injections; then two weeks' rest between series and such treatment continued as long as improvement was evident. Marks considered that this

method of therapy gave as good results as anything else he had tried, but I have seen no record of anyone else employing it.

Surgery.—It is the consensus that the involved glands should not be removed for the reason that draining sinuses and lymphedema are likely to result; of course in some instances the resection of polypoid, pedunculated tumors, and even of a vulva that has become elephantoid, may be advisable. Greenblatt and Wermer (1945) said very positively that fluctuant bubos should be aspirated and never incised, and that is certainly the consensus; however, there are some observers who feel that nowadays with the employment of sulfonamides they are doing better with incision and drainage. The subject of the surgical treatment of the rectal strictures was very thoroughly covered by Wright *et al.* (1946) in a résumé of their experience in 476 cases; the paper is commended to the especially interested reader.

NONTUBERCULOUS URINARY TRACT INFECTIONS

(Cystitis, Pyelitis and Pyelonephritis)

Sulfonamides.—Pool and Cook (1947), of the Mayo Clinic, found sulfathiazole and sulfacetamide as satisfactory as any of the other sulfonamides in the treatment of urinary tract infections, though they said that they used the other agents of the group frequently with good results. It was stated by these observers that doses beyond 30 to 40 grains (2 to 2 6 gm.) daily are seldom indicated; with this dosage, and a fluid intake of at least 2000 to 2500 cc. a day, renal complications are infrequently encountered. But the patient should be watched closely for any signs of toxic reaction: cyanosis, nausea and vomiting, fever or cutaneous reactions, headache, vertigo, malaise and weakness. These latter, beginning with headache, do not necessarily require that administration of the drug be stopped but they do require that a careful observation of the patient should be continued. Under the usual circumstances reduced renal function does not contraindicate the use of the sulfonamides. These agents are considered to be effective against most of the gram-negative organ- ... of the gram positive cocci with the

for example, one patient who had a mixed infection of coccus and ... became asymptomatic on sulfacetamide, the bacilli disappeared, but the cocci persisted; when changed to sulfathiazole, the remaining coccus infection cleared up. The reverse of this also occurred in the series: a patient who improved symptomatically and in whom the cocci disappeared on sulfadiazine, but in whom it was necessary to change to sulfacetamide in order to clear the bacillus infection.

The following matters warrant consideration in connection with sulfonamide therapy: (a) Cases in which there is a drainage tube in place will clear ... until drainage ceases. ... in- ... he ... (d) urinary channels, and particularly stones, ... Any considerable amount of stasis along the tract (stasis is the *important* etiologic factor in the infections of pregnancy) will prevent sterilization, but

it is said that the urine can be freed of bacteria even if there is a retention of as much as 3 ounces in the bladder; it requires less stagnation than this in the pelves and ureters to interfere seriously with the action of the drugs. (e)

drug to escape so completely through the uninfected functioning kidney that an effective concentration in the affected kidney is not obtained.

Penicillin.—Pool and Cook (1947), of the Mayo Clinic, said that they had given penicillin a complete trial and had found that in certain cases of staphylococcic infections, and sometimes in infections with *Streptococcus faecalis*, it has value when used in high dosage, however, in the usual gram-negative infections it is of questionable value in their opinion This is certainly the consensus But perhaps increasing experience will show penicillin to be of value as adjunctive therapy to the sulfonamides. Prince (1946) reported a series of thirty-six cases of transurethral prostatic resection in which sulfadiazine and penicillin were administered in combination, sulfadiazine being given in 15 grain (1 gm.) dosage every six hours, beginning the day before operation, and penicillin in a dose of 20,000 units every three hours, beginning at 6.00 A.M. on the day of operation; both drugs were continued in the above doses for five to seven days usually. In this series 47.2 per cent of the patients were discharged from the hospital with sterile urine, these being the first cases, according to Prince, in the records of the Brady Urological Institute of the

. oxidation in the
, the urine. It is
efficacious only in infections caused by gram-negative bacilli or *Streptococcus faecalis* and is nowadays not often used except in sulfonamide-resistant cases, but Burns (1944) felt that since it is highly effective against *Streptococcus faecalis* it should always be the preferred drug in infections with this organism. Pool and Cook (1947) felt that the greatest advantage of mandelic acid is its low toxicity. It may be given in the form of the elixir, syrup or tablet. Acid-

fluid intake is reduced to 1500 cc. a day, but some men still like to use higher dosage—45 grains (3 gm) at six-hour intervals, four doses in the twenty-four hours Burns (1944) preferred to use it in the form of the syrup or the elixir. The average adult dosage of the syrup he stated to be 2 teaspoonfuls four times daily and of the elixir 1 teaspoonful four times daily. Many men like to use the drug in the form of calcium mandelate, which is tasteless and does not cause much gastro-intestinal disturbance; it is said that it will often also give a sufficiently acid urine so that acidifying salts need not be used with it. Helmholz's (1937) method of using this agent may serve as model procedure; for

hood of the development of fastness in the infecting organisms. Colby (1947), Hewitt (1947), and others have also referred favorably to the concomitant *employment of alkalies. Pool* and Cook (1947) said that latterly they have formed the opinion that the proper dose of streptomycin is at least 3 gm. a day for the first few days because most of the organisms in the urinary tract will *rapidly* alter their sensitivity to streptomycin upon being exposed to it. Ferguson and Hershey (1947) employed 0.2 gm. intramuscularly at two-hour intervals and do not believe that less than 5 gm. should be given in the ordinary course of treatment, perhaps even 10 gm. in cases of a severe nature.

[illegible]

is apparently an effective type of therapy in selected cases; Austen (1940) showed that absorption of appreciable amounts into the blood stream can take place when the drugs are administered by this route. The sulfonamides are also used in 0.8 per cent solution for continuous irrigation or lavage of *the bladder several times daily. Pinck et al. (1944) found that if sodium* citrate solutions are introduced for anticoagulant action in the tract at the same time as sulfonamides the bacteriostatic activity of the latter—at least of *sulfacetamide*, the drug they experimented with—will be nullified. *Erickson (1945)* used cetyltyridinium chloride (ceepryn) in a dilution of 1:10,000 *to 1:8,000* with results that seemed to be fairly satisfactory; the agent was *used routinely in 260* cases of renal pelvic lavage, ureteral catheterization, cystoscopy, bladder irrigation or instillation, and urethral dilation or in- [illegible] of any sort and in some [illegible]

potassium permanganate, 1:8,000-1:5,000; mercurochrome, 1:[illegible], [illegible]curophen, 1:10,000; gentian violet, 1:500; acriflavine, 1:8,000-1:6,000. Reynolds and Schulte (1943) felt they obtained good results from the installation twice weekly of 2 ounces of cod liver oil especially in patients with infected residual urines.

STONE IN THE URINARY TRACT

Kidney stones, or calculi, consist of amorphous collections of granules of [illegible]

may present as a foreign body obstructing the ureter. At times [illegible] fluctuating aching pain in the loin of the affected side, or radiating into the lower back, the abdomen, or leg. Constant or intermittent hematuria is oftentimes remarked, and sometimes there is the passage of "sand." Bladder symptoms, such as frequency, urgency and burning, are not unusual even when the bladder is free from lesions. The most characteristic manifestation of the presence of stone, however, is an attack of renal colic. The pain strikes quickly in the kidney region, but soon radiates down into the abdomen, the thigh and [illegible] kidney region

[illegible]

days, but probably [illegible]

complete obstruction occurs there will be hydronephrosis on the affected side and perhaps anuria, even though the opposite side is not obstructed (the so-called "reflex anuria"). Thus, the symptoms of renal lithiasis are the symptoms of obstruction, but why the stones form in the first place is one of the most venerable of medical mysteries. The disease is unilateral in most cases, but at the present time there is no way of foretelling the tendency in a patient to develop stones on the other side Stones in the bladder may be either kidney stones halted there by obstruction, or they may originate there as deposits on some introduced foreign substance or as encrustations on inflammatory lesions. In general the symptoms of stone in the bladder are not very characteristic. The most usual complaints are of frequency, hematuria, the passage of sand, difficult urination, sudden stoppage in the flow of urine, and pain running down to the head of the penis. Tuberculosis, prostatic enlargement and vesical neoplasm must be carefully ruled out.

The earliest known urinary calculus was found among the pelvic bones of a boy about sixteen years of age in an Egyptian grave of a period some time prior to 4800 B.C. The treatment of vesical stone was made a specialty early in the Middle Ages by quacks who "cut" only for stone, most of the operations being performed on children, and these operative procedures were not effectively got out of their hands until the sixteenth century. In our present era, vesical calculus is predominantly a malady of elderly men, at least in the highly civilized countries, but it is said to occur still with great frequency in the young in hot dry climates; Pierce and Bloom (1945) reported that in a desert area in which the incidence of stone was high in the natives it soon became high in American troops also, though they were eating the standard American Army diet. Urinary calculi occur much less frequently among Negroes than among whites; the incidence in all races is said to be very low in wet tropical countries, though it was said by Glazier and Olson (1944) to have been rather high in the South Pacific area during War II under battle conditions in which there was excessive perspiration and a reduced fluid intake with resultant highly concentrated and highly acid urine. According to Lassen (1943), the world's chief stone areas are the Valley of the Volga River, Mesopotamia, Persia, Afghanistan, Turkestan, Northwestern and Eastern India, the Netherlands Indies, South China, Canton, Japan, and North and Eastern Africa.

Apparently Domenico Marchetti, in 1633, performed the first operation for renal calculus.

THERAPY

I shall not review all the diverse views regarding the etiology of stone because to do so would require a great deal of space and perhaps in the end really not much enlighten the reader. However, the possibility that Randall (1944) is correct should be mentioned. he says that no matter what dictates the deposition of particular salts, there is in every case of primary renal calculus a typical microscopic pathologic process in the wall of the renal papilla that precedes the gross appearance of stone—and he has convinced himself at least that this is true.

Fluids.—The opinion is unanimously held that the forcing of fluids is indicated for all kinds of stone since the more dilute the urine the less chance there is for precipitation of salts to occur Contrary to prevalent opinion a dilute urine does not preclude an acid urine.

Infection and Stasis in the Urinary Tract.—Both these conditions are known to contribute to calculus formation. Fortunately the sulfonamides are effective against the *common urea-splitting organisms* that enhance the precipitation of phosphates and carbonates by increasing the alkalinity of the urine. Stasis is a matter often requiring the most expert urologic handling.

Hyperparathyroidism.—The position of Albright and his group at the Massachusetts General Hospital has been that the development of renal calculi is a much more frequent and important consequence of hyperparathyroidism than are osseous lesions, but the profession as a whole has been slow to accept this concept. However, the paper of Cook and Keating (1945) reemphasized the relationship between hyperparathyroidism and renal calculi, for in a deliberate search for hyperparathyroidism at the Mayo Clinic during a period of eighteen months, they found eighteen cases in thirteen of which renal calculus was the presenting symptom and in the majority of which evidence of bone disease was minimal or absent.

Vitamin A Therapy.—The Council on Pharmacy and Chemistry, in 1947, still does not accept the contention that high vitamin A feeding is of value in dissolving and preventing the recurrence of stones.

Precautionary Measures During Recumbency or Immobilization.—It is now agreed that an active individual who has been using calcium constantly in renewing bone structure is in danger of developing stone when he becomes [illegible]

ash diet to be discontinued if the urine remains alkaline due to any cause (for an acid-ash diet not only keeps salts in solution but may *liberate them* from the bones, and such salts would precipitate in alkaline urine); (c) control of stasis by movement of the patient, provision of adequate drainage by catheter or surgery *if* necessary, and *maintenance of large fluid output;* (d) control of infection through maintenance of large fluid output, adequate drainage, and chemotherapy; (e) continuation of treatment for three months *after immobilization has ceased in order to remove* any small precipitation that may have formed during the period of stasis and hypercalcinuria; (f) early and frequent radiographic checkup examinations during the illness and every three months for one year thereafter.

Dissolution by Retrograde Irrigation.—In recent years the group about Albright at the Stone Clinic of the Massachusetts General Hospital has been studying the possibility of dissolving stones by irrigation with a citrate solution from below. Their early solutions were too irritating, but Suby and Albright (1943) devised their "solution G" with which they effected the *partial or complete* dissolution of calculi in six cases. The main object of treatment with this solution is to keep it in contact with the stone as *much as* possible; of course the details of the actual type of irrigating tube and the like by which this is accomplished belong in the field of urological surgery. Suby and Albright made the point very *emphatically that before attempting* to dissolve a stone with their solution it is necessary to know that one is

actually dealing with a phosphatic stone, by which is meant one composed of calcium phosphate with or without calcium carbonate or magnesium-ammonium-phosphate or both. Abramson (1943) reported the successful employment of this irrigation method in dissolving a large bladder calculus

Solution G (Suby and Albright, 1943)

Citric acid (monohydrated)	32 25 gm.
Magnesium oxide (anhydrous	3 84 gm
Sodium carbonate (anhydrous)	4 37 gm.
Water to make	1000 cc.

[illegible]

radium reactions in the bladder of the sort that are frequently complicated by formation of alkaline incrustations at the site of the ulceration, and said that the results accomplished "were impressive." These latter observers, however, felt it difficult to evaluate the extent to which improvement in their patients was due to the direct antimicrobial action of solution G. Flocks (1946) considered this type of irrigation an important part of the treatment of calcium phosphate stone, but Keyser (1945) said that after a ten-year experience most dissolution technics have been found disappointing

Uric Acid Stones.—The treatment consists in using an alkaline-ash diet because the urates thus formed are more soluble than uric acid itself. Many [illegible] the usual practice is to

[illegible] is soluble both in acids and alkalis, nothing is to be expected from an attempt to change the reaction of the urine. Fluids are to be pushed It is the practice in some quarters to prescribe a diet low in oxalates, but I do not know how many men are willing to guarantee nonrecurrence of the stone as a result of using it

Cystine Stones.—The patient with cystine stones is the victim of an hereditary disturbance in cystine metabolism. Cystine precipitates in an acid urine, so the treatment consists in using an alkaline-ash diet.

Estrogens and Aluminum Hydroxide Gels.—Shorr (1945) proposed the use [illegible]

phate, calcium carbonate, magnesium phosphate, magnesium-ammonium phosphate, and calcium-magnesium-ammonium phosphate. He felt that his own data did not warrant the drawing of conclusions but made the report in order to stimulate a wider exploration of the possible utility of these measures

Diets.—The several diets referred to above are the following. *Acid-ash:* meats, fish, eggs, cereals, little fruit and vegetables, no milk or cheese. Albright seems to feel nowadays that the adult, particularly if he is sedentary, should [illegible]

spinach, tomatoes, beets, endive, rhubarb, asparagus, strawberries, rasp-

berries, pears, plums, figs, currants, cocoa, chocolate, tea and sweets in general. MacDonald (1936) favored the use of hard cider for its malic acid content.

Spa Treatment.—The drinking of large quantities of water, frequently referred to above, has been asserted to be of value since ancient times. Certain mineral springs, of which every continent has its favorites, are said to have the power to fracture stones, with the fragments being ultimately passed, at the least, much water is drunk at the spas and the music is often most enjoyable.

Surgery.—There is nothing to say in a book of this sort of course except to lament under this head the fact that a woefully large proportion of the victims of stone must still submit ultimately to instrumental or operative interference. Recurrence, however, is as much a bugaboo to the surgeon as to the internist.

Renal Colic.—In the presence of severe pain, morphine sulfate, $\frac{1}{4}$ grain (15 mg.), or dilaudid, 1/32 grain (2 mg), combined with atropine sulfate, 1/100 grain (0 6 mg.), is given hypodermically; often the opiate has to be repeated and frequently will not relieve this pain at all. The new drug demerol, with its ability to relieve smooth muscle spasm, may be expected to win a place for itself in the treatment of this type of colic; average dosage is $2\frac{1}{2}$ grains (150 mg.). Morrissey (1947) used a proprietary tablet (donnatal) containing $\frac{1}{4}$ grain (15 mg.) of phenobarbital and belladonna alkaloids equivalent to $\frac{1}{2}$ grain (30 mg.) of belladonna leaves, in a dosage of two tablets at the onset of symptoms and two tablets every two hours thereafter, but not to exceed four such doses a day, until relief was obtained. He found the use of this preparation superior to the use of atropine alone. Bauer *et al.* (1931) injected 20 cc of 5 per cent calcium chloride solution intravenously in a small series of cases, in nearly all instances relief was prompt and great enough to permit the patient to go to sleep without an opiate; in one case calcium chloride injection succeeded where morphine had failed. Fleischman (1939) also reported success with the use of calcium chloride injections in a number of instances. Lund and Zingale (1943) used a synthetic antispasmodic, octin, with some degree of relief in a large proportion of their patients. Pennington (1945) also used this drug with good results in more than 200 cases of pain resulting from spasmodic phenomena in the genito-

used an intramuscular injection of 1 cc. Side effects seen by him in a few cases consisted in a feeling of faintness in one patient, a heat flush in another, nausea in one, and slight vertigo in several others. Heat, best applied by placing the patient in hot water in the bath tub, is often effective in relieving this pain, but some individuals are in such agony that they cannot remain in the tub. Sometimes resort to general anesthesia is necessary. Florence *et al.* (1946) found intravenous urography of considerable diagnostic value in twenty-three patients during episodes of colic, giving information far beyond that obtained from survey roentgenograms

DISEASES OF THE NERVOUS SYSTEM

SYDENHAM'S CHOREA

(St Vitus' Dance)

Chorea is one of the common diseases of childhood. It may occur at any age but most cases are seen between the fifth and fifteenth years. The dis- [illegible] than i [illegible] rarely [illegible] e, the parent usually states that for a week or more it has been fidgety, emotional and excessively clumsy Upon observation the patient will be seen to be in almost constant jerky motion, grimacing and purposeless movements of the face and head are the most usual phenomena, but any part of the body may share in the wriggling or writhing motion There is also much muscular incoordination, as shown frequently by the overpassing of objects with the hands or by difficulties in locomotion Except in the most severe cases, these movements cease during sleep and are to some extent under voluntary control; at least firm, kindly commands will often cause them to be restrained for a brief space The speech is often choppy in character, sometimes being entirely unintelligible; in a relatively few cases the child is entirely unable to speak. The usual mental involvement is in the direction of dulness, carelessness and loss of memory, though not infrequently this state is broken into by intense emotional storms. Appetite and the general condition usually remain good despite some loss of weight and the development of more or less anemia. Headache and muscular weakness are always complained of. The duration varies from several weeks to many months, sometimes to more than a year. Death from chorea itself, if one can speak of it as an entity, is very rare, but it is well to bear in mind that even mild attacks may be associated with severe rheumatic heart disease Relapses and recurrences are not uncommon.

Since the middle of the last century the effort has been made, both in Europe and America, to link together rheumatic fever and chorea. Undoubtedly the presumptive evidence in favor of such an association has great weight and most men have accepted it. However, Wheeler (1947) said he often sees cases diagnosed as chorea in adults in which he is not certain that the syndrome is a manifestation of rheumatic infection Gold (1947) made the point that one is unlikely to see a long-standing case of Sydenham's chorea without elevated sedimentation rate, leukocytosis or fever.

Sydenham provided the classical description in 1686 During the early part of the [illegible]

THERAPY

Wilson (1947), though looking upon chorea as a manifestation of rheumatic fever in practically all instances, does not use the salicylates in treatment but relies instead upon sedatives and bed rest; [illegible]
ally codeine [illegible]
protective si[illegible]
occasionally [illegible]
in swallowing In protracted cases especial attention should be given to the dietary to see that it is well balanced and contains easily digested foods; vitamin supplementation, perhaps especially with vitamin C, is desirable. Elghammer (1946) said that he has often found warm baths or warm packs twice daily to be very beneficial. He made the point also that the inducement of purposeful movements, such as attempts by the patient to feed himself, to handle objects, and to walk around the bed, shortens the period of incoordination and muscular weakness.

Arsenic, nirvanol and fever therapy have all been abandoned by practically everyone. Arsenic, because long experience showed that it really had no value; nirvanol, because it was highly toxic and probably accomplished nothing more than a fever reaction; and fever, for the reason that the treatment was often harder on the patient than chorea itself.

HICCUP

Hiccup is produced by a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis. It occurs not infrequently in the fetus, detectable as regular, short, quick jerks at the rate of 15 to 30 a minute; they are visible and palpable, and the muscle sound of the diaphragm as well as of the body striking the uterine wall can be heard. If occurring during labor it is sometimes not interrupted by the birth of the child and continues for a short time afterward; babies have been born hiccuping so loudly that they could be heard in the next room. McGee (1943) felt that fetal hiccup indicates that the child will in all probability be a very allergic infant. The greatest incidence of hiccup in infancy occurs during the first three months, principally among breast-fed babies, probably due to overdistention of the stomach with food and swallowed air. In adults it may be caused by inflammatory or pressure irritation of the phrenic nerve or reflexly through the vagus. It may be a symptom of almost any disease but the entities with which it is most often associated are neurosis, epilepsy, encephalitis, brain tumor, Addison's disease, and functional, organic, traumatic and acute infectious processes anywhere in the gastro-intestinal tract. Apparently it also occurs reflexly in diseases of the pleura and pericardium as well as in some of the chronic constitutional diseases. And some surgeons of experience used at least to look upon the occurrence of postoperative hiccup as a warning of impaired renal function. Byrnes (1935) described some cases apparently occurring as an unusual form of tabetic crisis. In addition to which there are the idiopathic and epidemic cases, the latter believed by MacNalty (1937) to be manifestations of epidemic encephalitis of a mild type.

THERAPY

Most cases in infants are transitory and of no serious importance. The infant should not be permitted to suck the breast when it is empty or the

fruit juice Of course the more serious cases may also be seen in infants. In adults the most important thing, of course, is to make every effort to locate and treat the underlying cause of the trouble, which is very much easier to say than to do. The actual measures directed against the spasms are of course legion, as is the case in all maladies of vague and variable etiology; the following seem most often to have been of assistance.

Sedatives and Anesthetics.—The whole gamut is run—bromides, chloral, barbiturates, paraldehyde, belladonna, compound spirits of ether (Hoff-

results in intense momentary pain, oftentimes promptly stops an attack. Deep anesthesia is sometimes successful, but it was induced with both ether and chloroform in Campbell's (1940) case without effect either time.

Carbon Dioxide

livered from the

number of times

inducing the inhalation of carbon dioxide, which has been much used by others since. An ordinary paper bag of medium size and strength is placed over the

one of them had been hiccuping for two days.

Nikethamide (Coramine).—Schell (1947) said that the intravenous in-

on patients who had become refractory to the inhalation of carbon dioxide.

Fluids.—In postoperative cases in which impaired renal function is suspected, the "pushing" of fluids not infrequently brings relief.

has

P

sort

success.

TRIGEMINAL AND ASSOCIATED TYPES OF NEURALGIA

comes "out of a clear sky," and is described as shooting, stabbing, lightning-like, cutting, etc. It lasts but a few seconds to a few minutes, but during the time of its presence is perhaps as severe as any that man is ever called upon to endure. The patient remains motionless with a fixed grimace and oftentimes with some defensive posture of the body as a whole. Relief is usually complete upon termination of the spasm. Such an attack may be precipitated by any minor essential movement, such as opening of the mouth, swallowing, winking, talking, washing the face, brushing the teeth, and so on. In the beginning there is often a considerable interval between seizures, and there may even be an asymptomatic period of several months to years, but finally in practically all cases the pain becomes continuous and affects all three divisions of the nerve. It is my belief that spontaneous recovery has never been recorded. In Horrax's (1946) series of cases, 3 per cent of the patients had tic on both sides of the face. In untreated cases, death may result from inanition consequent upon inability to eat or sleep. Rarely, very careful general and neurologic examination will be required to rule out peripheral lesions as the cause of this type of pain—lesions involving the nerve trunks, posterior roots or root ganglia, lesions of the brain stem or in the optic thalamus, lesions in higher associated brain centers. Woltman (1942) pointed out that tumors of the gasserian ganglion are not common but that when they occur the pain is usually constant and intense and not influenced by eating, speaking, or external irritation, and as a rule paresthesias and sensory changes appear relatively early. Typical of the sort of pseudotrigeminal neuralgia that may be encountered is the case of Banyai (1936) in which pain was completely relieved by phrenic nerve block and was thought to have been referred to the trigeminal nerve from the site of a tuberculous diaphragmatic pleurisy.

Tic douloureux involving the glossopharyngeal nerve is manifested as pain extending from the tonsillar region into the ear; relief of pain upon cocainization of the nasopharynx establishes the diagnosis. Tic involving occipital nerves arising from the first, second and third cervical nerves is differentiated through relief achieved upon procaine infiltration beneath the scalp. Other, very rare, types are those known as Sluder's, Jacobson's and Hunt's neuralgias.

Trigeminal neuralgia, by far the most frequently encountered of these maladies, is almost always a disease of those in or past the middle years of life, though Harris (1943) said he had had more than twenty patients who began to suffer before the age of twenty-one—two of them at the age of [illegible] and one at the age of sixteen months. It is a disease of unknown [illegible] often been remarked; [illegible] it rare. The entity was [illegible] called "the Prince of Physicians" at the court of more than one caliph at Bagdad, about the year 1000 of our present era, the first accurate description satisfying the present-day criteria was that of Fothergill, in 1773

THERAPY

The Older Analgesics.—None of the sedatives or analgesics is consistently of value in trigeminal neuralgia save only opium, and even it must be given in

rapidly increasing doses in order to control the pain; it is therefore used only when trichlorethylene fails and surgical relief cannot be obtained or is refused. It is also stated in the older literature that doses of N.F. tincture of aconite sufficient to cause considerable lethargy and a slowing of the pulse to 50 or less, *i.e.*, beginning with 15 minims (1 cc.) three times daily and increasing, will sometimes afford temporary and partial relief.

Trichlorethylene.—The present method of administration of trichlorethylene, a sweet-smelling colorless liquid, is to break one of the 1 cc. ampules in which it is available in a handkerchief and inhale while lying down (slight dizziness and drowsiness are occasionally caused) until there is no more odor; this three or four times daily for a period of four to six weeks. In those obtaining relief, it is the practice to continue the treatment by inhaling on th- consecutive days every two or three months. Horrax and Poppen (193 stated that of their ninety patients nearly one-half obtained sufficient reli that they did not feel obliged to submit to more radical treatment for period of six months up to six years, in the other patients injection or surgery had to be resorted to very quickly. An advantage of the drug, which would seem to make its trial worth while in any beginning case, is that it does not cause local numbness, as do injection or the surgical procedures. There are many cases of severe poisoning on record as a result of prolonged contact with the drug industrially, but these things need not be feared when it is used therapeutically. However, Eichert (1937), and Walker (1945), recorded cases in which the use of grossly excessive dosage caused very alarming mental symptoms or coma of several days' duration.

Typhoid Vaccine.—Paull (1946) reported the successful relief of symptoms in a patient through the intravenous administration of triple typhoid vaccine upon three occasions, spaced respectively at eighteen months, eighteen months, and sixteen months. He felt that a starting dose of approximately 5,000,000 organisms is sufficient, increasing the dose if necessary as the patient's tolerance indicates, and that one should be especially cautious with debilitated or aged patients or patients with blood dyscrasias or vascular or renal disorders. The patient should be at absolute rest under close observation until the reaction has disappeared, and the injections should never be administered more frequently than at intervals of forty-eight hours in order to avoid a very serious type of reaction. This sort of treatment has been mentioned once or twice before in the earlier literature and perhaps should be given a thorough study.

Alcohol Injection and Surgical Treatment.—The surgical measures available at the present time for the relief of trigeminal neuralgia are: (a) alcohol injection of the nerves near the foramina of exit from the skull; (b) alcohol injection of the gasserian ganglion (which Maxwell, 1946, said may be very dangerous and in the majority of instances is impossible of performance), (c) the operation of peripheral avulsion of the sensory root, (d) radical division of the sensory root, (e) an intramedullary tractotomy; (f) supraorbital and infraorbital peripheral neurectomies. All of these measures have their advantages and disadvantages, their advocates and detractors. I believe the selection of the type of treatment to be employed in a given case is so serious a matter that it should not be treated of merely in passing in this book, even were I qualified to do so. However, I permit myself to counsel the reader to entrust his patient only to a surgeon who has had much cadaver and actual operative experience in these matters. Horrax (1946) said that in his experi-

TRIGEMINAL AND ASSOCIATED TYPES OF NEURALGIA

Trigeminal neuralgia is a disease of the gasserian ganglion, affecting one or all of the branches of the trigeminal nerve; the infra-orbital division is the most frequently affected, then the mandibular and then the ophthalmic. The pain comes "out of a clear sky," and is described as shooting, stabbing, lightning-like, cutting, etc. It lasts but a few seconds to a few minutes, but during the time of its presence is perhaps as severe as any that man is ever called upon to endure. The patient remains motionless with a fixed grimace and oftentimes with some defensive posture of the body as a whole. Relief is usually complete upon termination of the spasm. Such an attack may be precipitated by any minor essential movement, such as opening of the mouth, swallowing, winking, talking, washing the face, brushing the teeth, and so on. In the beginning there is often a considerable interval between seizures, and there may even be an asymptomatic period of several months to years, but finally in practically all cases the pain becomes continuous and affects all three divisions of the nerve. It is my belief that spontaneous recovery has never been recorded. In Horrax's (1946) series of cases, 3 per cent of the patients had tic on both sides of the face. In untreated cases, death may result from inanition consequent upon inability to eat or sleep Rarely, very careful general and neurologic examination will be required to rule out peripheral lesions as the cause of this type of pain—lesions involving the nerve trunks, posterior roots or root ganglia, lesions of the brain stem or in the optic thalamus, lesions in higher associated brain centers. Woltman (1942) pointed out that tumors of the gasserian ganglion are not common but that when they occur the pain is usually constant and intense and not influenced by eating, speaking, or external irritation, and as a rule paresthesias and sensory changes appear relatively early. Typical of the sort of pseudotrigeminal neuralgia that may be encountered is the case of Banyai (1936) in which pain was completely relieved by phrenic nerve block and was thought to have been referred to the [illegible] pleurisy

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THERAPY

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combined with the salicylates as used in the treatment of acute rheumatic fever, the case is often controlled, though it is doubtful if these procedures lessen the total duration of the attack. Codeine sulfate, 1 grain (60 mg.), or even full doses of morphine or dilaudid, must sometimes be used in the beginning of very severe cases. Counterirritants are not beneficial, and massage in the acute stage only aggravates the symptoms. Oftentimes it is helpful to place boards over the springs of the bed and to use a mattress of the pad and not the spring type above them. Buck's extension, with 8 or 10 pounds, may be useful in some cases though the pain is often exaggerated in the beginning. The opposite type of treatment also sometimes succeeds according to Colt (1944): the patient lies on his back, well relaxed, with the knees bent over a large firm pillow and presses firmly on a vertical bed-board with the ball of the foot of the affected side, the ankle being dorsiflexed. It is said that short wave diathermy oftentimes relieves this pain, but Dalton (1944) found that during the acute stage the exertion of reaching the physiotherapy department often more than counteracted the beneficial effect of the treatment.

Some men feel that manipulations of the "osteopathic" type are distinctly helpful in selected cases; it would seem that a good many patients found this out for themselves long ago. Many times, after a patient becomes ambulatory, an especially devised corset or belt is prescribed for him, possibly he is even sometimes helped by the gadget.

Prolapsed Disk Operation.—In 1943, Hurst of Guy's Hospital, in what he called a "debunking" essay on the treatment of sciatica, took the position that the few patients who do not get well after a month of complete rest in bed are in most instances those who need to be referred to the neurosurgeon who will cure them by removal of the herniated intervertebral disk. But the flood of letters "to the editor" of the British Medical Journal that followed the appearance of his paper indicated that there are not many in the profession who are so willing to make a facile classification of patients into those who need rest and psychotherapy and those who require obligatory surgery. Dunning (1946), comparing the results of surgical and conservative therapy at the New York Hospital, found that recovery occurred without operation in 54 per cent of the cases, but that operation had bettered the prognosis by 32 per cent. However, there are surgeons who are even going so far as to admit that recurrences are very frequent after the operation.

Injection Treatment.—It is claimed that many severe cases of sciatica may be reduced in duration to only a few days by injection of physiologic saline solution or oxygen or procaine.

The technic of the simple saline injection of the nerve in the buttocks was described by Burt (1939) as follows: "The patient lies on his face and a pillow is placed [illegible]

tion is confirmed [illegible]

the solution (10 cc. of 1 per cent novocain made up to 100 cc. with physiologic saline solution) very slowly and leaving the needle in position, refill the syringe.

ence at the Lahey Clinic the average period of relief experienced as the result of alcohol injection is about a year and a half, though many patients are relieved for much longer periods. He felt that if the nerve is entered satisfactorily by going through the scar tissue resultant upon the first injection, the relief obtained by subsequent injections will be just as sure and as lasting as that following the first injection. An important function of the alcohol injection in Horrax's opinion is to demonstrate to the patient the feeling of numbness or anesthesia that he will be obliged to have permanently if the sensory root or a portion of it is subsequently divided, and he considers this such an important consideration that it is his almost invariable rule to insist that every patient should have at least one alcohol injection before undergoing the radical operation. Injection and surgical procedures are likewise available nowadays for the other rarer types of neuralgia mentioned above.

SCIATIC NEURALGIA

The majority of the victims of sciatica are males between the ages of thirty and sixty years. In most cases the pain begins in the sciatic notch or in the lower lumbar region and gradually extends down the course of the sciatic nerve. In the beginning this pain is often merely a dull ache that bothers the patient very little, but it finally becomes burning, sticking, or lancinating in character, and radiates downward from the sciatic notch along the posterior aspect of the thigh into the calf muscles and foot. In many chronic cases the pain is ultimately confined to the outer aspect of the calf and foot, where it becomes persistent and causes as much discomfort as the pain in the thigh and buttock during the early stages. Tender spots and areas of paresthesia are frequently noted Some individuals find the reclining position on the unaffected side, with thigh and leg slightly flexed, absolutely essential for partial comfort, while others, particularly in the later stages, find walking gives greater relief. An attack of sciatic neuralgia may be relatively mild and persist for only a few days, but severe cases are protracted for weeks to months, during which time the patient is entirely incapacitated and suffers severely. Recurrence is the rule.

Pain due to visceral pelvic disease, sacro-iliac strain, arthritis of the lumbar spine and of the lumbosacral and sacro-iliac or hip joint, anatomic anomalies, and pelvic and cord tumors must be ruled out in every case of suspected sciatic neuralgia.

THERAPY

Removal of Foci of Infection.—Whatever may be the true cause of sciatica, *i.e.*, whether it be a ganglionitis, a periganglionitis, a neuritis, or an "idiopathic" neuralgia, it is claimed by some men that it is of paramount importance to eliminate all possible foci of infection whenever sciatica is diagnosed. Consequently a huge mound of teeth has piled up outside the jaws of American citizens in recent decades; I wonder how much sciatica has been cured.

Rest, Analgesia and Physical Therapy.—In the early stage of an attack, complete rest in bed and the application of some form of heat along the course of the nerve, especially in the gluteal region, are efficacious measures. If

changed to "endolymphatic hydrops" in order to dispose of the fallacious belief, engendered by one of Ménière's unfortunate early reports, that bleeding into the semicircular canals takes place in this entity.

THERAPY

Low Sodium-High Potassium.—Furstenberg *et al.* (1934) reported good results with a diet of low sodium content coupled with the intermittent ingestion of ammonium chloride. This treatment not giving great satisfaction in the hands of all workers, Talbott and Brown (1940) proposed the use of a diet of

matter of low sodium-high potassium regimens is discussed fully in Chronic Nephritis.) All except a few of Talbott and Brown's 40 patients were reported sufficiently helped by this regime to be able to live relatively normal lives, but

the potassium chloride of Talbott and Brown—in conjunction with a low sodium diet. It is not evident from their data that superior results were obtained with this regime.

Low Sodium Diet.—Avoid all of the following: all salt meats and fish and bread, crackers and butter prepared with salt, carrots, clams, condensed milk, raisins, caviar, cowpeas, olives, spinach, cheese, endive, oysters. Take the following no more than twice weekly: lima beans, beets, buttermilk, cantaloupe, cauliflower, celery, chard, dried coconut, dried currants, dates, figs, horseradish, kohlrabi, limes, muskmelons, peanuts, peaches, mustard, pumpkin, radishes, rutabagas, strawberries, turnips, turnip tops, watercress. Of course all food is to be prepared and served without salt.

that they were not satisfied with the improvement. Some had received no benefit." Some patients seem to get along for months with only the one injection or a few such injections in daily succession in the beginning. For maintenance, Horton suggested 0.1 to 0.2 mg. of histamine base subcutaneously two to four times a week, but Rainey's (1943) experience led him to doubt the value of such maintenance dosing. Atkinson (1944) felt that only one in five or less patients belonged to the group in which relief may be expected from the use of histamine.

Niacin (Nicotinic Acid).—Atkinson (1944) said that 12 per cent of 100 patients treated with niacin as a vasodilating agent had been completely relieved and 40 per cent improved. Williams (1945) reported that fifty of his sixty-two patients were relieved. The method of employment consists in

Having fixed the syringe in position, slightly withdraw the needle and push upwards into the piriformis muscle and inject a further 50 cc. Even if the saline does not penetrate the sheath of the nerve relief may be obtained."

The technic of oxygen injections was described by Brown (1944), who did not, however, claim originality for it: oxygen is injected from a cylinder via a wash bottle with warm water into the subcutaneous tissue over the sciatic nerve until the surrounding tissues are thoroughly distended and ballooned, when the needle is withdrawn and the process repeated lower down. When the emphysema has disappeared in the course of two or three days the same process is repeated.

Price (1944), who said that he had injected local anesthetics with satisfactory results in about 800 cases, proceeded as follows: the aim is to inject into the foramen where acute tenderness is produced upon deep pressure by means of a probe; the hypodermic needle is inserted to a distance of about 1 inch before making the injection. The treatment is always reinforced by active forcible exercises, and it was stated that determined patients who persevere with the exercises for the rest of their lives do not suffer from recurrences.

MÉNIÈRE'S DISEASE

(Endolymphatic Hydrops)

This is a malady characterized by recurring attacks of deafness, tinnitus, nausea and vomiting, and dizziness in which objects rotate or jump rapidly. It is believed that Martin Luther was suffering one of these attacks when he hurled the famous ink-pot at the Devil who was plaguing his ear. Ménière's description established the clinical entity in 1861, but to date all pronouncements regarding its causation are still largely speculative Atkinson's hypothesis is that the attacks result from vasomotor disturbances that are in some instances allergic in nature and possibly migraine equivalents; the Furstenberg diet and its later modifications resulted from reinvestigation of the proposition made some years ago by Danish observers that a waterlogged labyrinth associated with disturbances in salt and water metabolism underlay the disturbances; Talbott and Brown have held partial depletion of tissue [illegible] Horton and his associates believe that the disturbance [illegible] meability of the capillary [illegible] byrinth being a site most frequently involved with tinnitus and diminution of hearing evidencing secondary cochlear involvement; Williams' concept is that Ménière's disease is a form of physical allergy. Practically all of the victims of Ménière's disease are in or past middle life; the left side is more often affected than the right. The onset of the attack is usually very sudden and violent; the patient may be incapacitated for a few seconds, a few hours, or a few days, but between attacks he is usually completely free from symptoms. Williams (1945), reviewing the fourteen cases that had come to autopsy throughout the world, said that there had been revealed in them an unvarying pathologic picture of a non-inflammatory distention of the endolymphatic system affecting chiefly the scalamedia (ductus cochlearis) and the saccule and utricle. Woltman, according to Williams, has felt that the name of the disease should be

changed to "endolymphatic hydrops" in order to dispose of the fallacious belief, engendered by one of Ménière's unfortunate early reports, that bleeding into the semicircular canals takes place in this entity.

THERAPY

Low Sodium-High Potassium.—Furstenberg *et al.* (1934) reported good results with a diet of low sodium content coupled with the intermittent ingestion of ammonium chloride. This treatment not giving great satisfaction in the hands of all workers, Talbott and Brown (1940) proposed the use of a diet of normal sodium content but proportionately higher in potassium. This regimen is very simple since it merely comprises the taking of a normal diet plus 6 to 10 gm. (1½ to 2½ drachms) of potassium chloride in aqueous solution daily. (The matter of low sodium-high potassium regimens is discussed fully in Chronic Nephritis.) All except a few of Talbott and Brown's 40 patients were reported sufficiently helped by this regime to be able to live relatively normal lives, but

sodium diet. It is not evident from their data that superior results were obtained with this regime.

Low Sodium Diet.—Avoid all of the following, all salt meats and fish and bread, crackers and butter prepared with salt; carrots, clams, condensed milk, raisins, caviar, cowpeas, olives, spinach, cheese, endive, oysters. Take the following no more than twice weekly: lima beans, beets, buttermilk, cantaloupe, cauliflower, celery, chard, dried coconut, dried currants, dates, figs, horseradish, kohlrabi, limes, muskmelons, peanuts, peaches, mustard, pumpkin, radishes, rutabagas, strawberries, turnips, turnip tops, watercress. Of course all food is to be prepared and served without salt.

vertigo, nausea and vomiting; less than half obtained improvement in tinnitus. Of these patients, twenty-five had previously undergone some form of Furstenberg treatment (see above) with some degree of palliative effect, "but the fact that they returned to the clinic for additional treatment indicated that they were not satisfied with the improvement. Some had received no benefit." Some patients seem to get along for months with only the one injection or a few such injections in daily succession in the beginning. For maintenanc

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giving daily intramuscular injections of 25 mg—building the amount up somewhat slowly if necessary—while at the same time giving from 50 to 100 mg. or more by mouth daily. It is said that in some instances patients are able to get on after a while with the oral administration only but that others continue to need an *occasional injection as well.* In addition to the use of niacin, Williams asks his patients to restrict their intake of fluid to the equivalent of six glasses of water a day and to take 6 gm. of potassium nitrate during each twenty-four hours in divided doses with meals.

Surgery.—It is almost universally conceded, I believe, that Ménière's disease can be *permanently cured by division of the auditory* nerve. In the *hands* of a specialist in this procedure the operative risk is exceedingly low; Dandy (1941) reported that he had performed 401 operations, with one death—the 358th case—due to meningitis. Grove (1941) felt that surgical intervention should be reserved for patients who have not responded to a medical regime or who for one reason or another cannot be kept on such a *regime; he felt that*
wh
of

MYASTHENIA GRAVIS

T ... ally occurring in children and even infants, this is usually
women as men. It is
the muscles, especi-
es cannot be opened,
there is difficulty in speaking, chewing and swallowing, and the head may roll about loosely. As the disease advances no amount of rest affords sufficient access of strength to break through the paralyses, but actual muscle atrophy is rare and the central nervous system does not really seem to be involved, though the entity is most conveniently studied among the diseases of *this* system. There are remissions in the course of myasthenia, but ultimately, after months or years, the patient becomes permanently bedridden and dies from exhaustion or pneumonia; in an occasional case, *however, the only* signs and symptoms are those referable to the ocular apparatus. The etiology of the disease is still unknown and in its early stages it is not always easily differentiated from neurotic disturbances; the ergograph, prostigmine, *quinine* and curare tests are, however, valuable diagnostic aids. Wilson and Stoner *(1944) produced a block in nerve-muscle transmission* with the serum of myasthenia gravis patients, and Torda and Wolff (1944) obtained results suggesting that there is a defect in acetylcholine synthesis in the disease, however, the full significance of neither of these findings is established as yet. Blalock *et al.* (1939) collected from the literature *fifty-three proved*
... associated with abnormalities of the thymus,
... e in which postmortem exami-
... *reported.* McEachern (1943)
... *nt or tumor is rarely found.*
Hereditary transmission or familial incidence has not been conclusively shown,
... such as those of Riley and Frocht
... patients were sisters,
... patient gave birth to
a myasthenic infant.

THERAPY

Educating the Patient.—Some years ago Boothby emphasized the importance of educating the patient. Instruction should include: (a) information

Rehfuss tube through the nose into the stomach for the administration of fluids and food.

That myasthenia in itself does not necessarily preclude successful pregnancy and labor was demonstrated by the patient of Adam (1946).

Prostigmine (Neostigmine).—In 1934, Walker reported the successful use of physostigmine in a patient in whom she had tried the drug because of the partial resemblance of myasthenia to mild curare poisoning, physostigmine being known as an antagonist in the latter condition. When prostigmine, an analogue of physostigmine with less effect on the eyes and heart, was introduced shortly thereafter, she also reported the successful use of this drug in a single case Then Pritchard (1935), and Laurent (1935), each reported effective use in seven cases, and the wide employment of the drug began. The mechanism of the action is still unexplained, for the assumption that prostigmine inhibits cholinesterase activity of an excessive degree remains gratuitous since available evidence fails to establish firmly any departure from the normal esterase values in the disease. However, a large number of reports have accumulated to show that this drug is very effective in quickly causing partial to complete disappearance of the typical symptoms during a relapse. Viets (1944), of the Massachusetts General Hospital, summarized his experience in 100 patients, some having been seen throughout an eight-year period and some observed for less than one year In the 100 cases there were twenty-two deaths in eight years, which Viets contrasted with the mortality of 70 to 80 per cent that he believed to occur before the introduction of prostigmine into therapy, he also stressed the point that the twenty-two patients who died were in the later years of life Particularizing the forty-five ambulatory patients seen during 1942–43, Viets stated that about half

that treatment must be highly individualized and that most patients cannot take enough prostigmine to be optimally maintained, though in a more recent report (1945) he said that in a few cases as little as ¼ grain (15 mg), divided into two doses during the day, suffices for control A little food should be taken with each dose in order to counteract smooth muscle stimulation. All of Viets' patients with respiratory distress have written instructions from his clinic regarding the use of prostigmine methylsulfate intramuscularly. Three or four of the forty-five patients above mentioned resorted to such injections a few times a year, two or three ampules of 0 5 mg. each being used at one time, with or without atropine sulfate Viets says their tendency

22 mg. orally and 0.75 mg. every other day intramuscularly. In several emergency situations in adults, Viets (1944) has given 1.5 to 3 0 mg. of the methylsulfate salt intravenously, adding it to dextrose solution and introducing it by the drip method during one hour.

Other Drugs.—Richter (1945), in referring to *guanidine hydrochloride*, introduced to supplement prostigmine by Minot *et al.* in 1939, suggested a dosage of 10 to 25 mg. per kg. (2.2 lbs.) body weight in three or four divided doses throughout the day; if the drug causes excessive gastro-intestinal symptoms they may be counteracted by the use of atropine, excessive nervousness and muscle twitching by calcium gluconate. Viets (1945) said that he has one patient who has taken nine tablets of 125 mg. each daily for many years with complete relief of her symptoms, but that many patients give up the use of the drug because of the annoying paresthesias it causes. Richter (1945) preferred *ephedrine sulfate*, in a dosage of 3/8 grain (22 mg.) twice or three times daily, as a supplementary agent, but said that if it causes nervousness, tachycardia or insomnia not eliminated by reduction in dosage, one must change to another drug. It was Viets' (1945) opinion that about half the patients find ephedrine useful, but he has no patient who is being maintained on it alone; he c

chloride, introdu

it may be used

effective, the dosage suggested being 10 gm. three times daily in eggnog. This agent may c

be combated by t

than 10 per cent

completely unrelated chemically to

n chemical warfare during War

wering cholinesterase activity. Comroe *et al.* (1946) reported its employment in seven patients with myasthenia gravis; two of these patients received little or no benefit, two were

the other two the effects

se

fluorophosphate equal that produced by prostigmine, and unfortunately attempts to give larger doses resulted in marked nausea and vomiting and symp-

matters

henia.

from

eding

of the

Massachusetts General Hospital fifteen patients had been subjected to thymectomy with an operative mortality of 26 6 per cent. Thymomas were

were in their second

report; two were considered in complete remission, two more distinctly improved, three moderately improved, one slightly improved, and three had been operated on too recently to evaluate. None of the patients had relapsed. Richter (1945) said he thought that many more cases would have to be studied and longer postoperative periods elapse before the true worth of this therapy would be known. He felt that if one could speak of indications for the pro-

whom
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nedical
management. Keynes (1946) said that the results he had obtained upon the whole justified the further performance of thymectomy, though I cannot refrain from adding that just two years before he had expressed the feeling that the surgeon is treading upon uncertain ground in this field

X-Ray.—Richter (1945) said that while the reported results of x-ray treatment have been very conflicting, there would seem to be no contraindication to trial of this type of therapy in selected cases, however, Viets (1945) said that after using x-ray treatment in fifteen cases and seeing no results, he had given it up.

MIGRAINE

vague or definite gastro-intestinal symptoms; or the attack may come on more suddenly following a period of one or more hours of exceptional well-being; or—and this is not infrequently the case—the patient may recognize a night of more than usually sound and refreshing sleep as a warning signal. In most cases the headache is ushered in by visual disturbances, these may be of the nature of flashes of light, or of wriggling threads of light that pass across the field of vision, or of definite loss of visual acuity, and they may disappear

lasts from a few hours to several days, the patient is sometimes more depressed or confused than can be easily accounted for by the distraught state

approaches; sometimes it disappears at puberty and returns at the climacteric. It often is absent during gestation, and may disappear for a long period after one of the acute infectious diseases. Nothing is known definitely regarding the cause of this strange malady, though the tendency is known to be almost certainly hereditary. The similarity between migraine and the recognized allergic group—hay fever, asthma, urticaria, angioneurotic edema, food allergy, etc.—has caused the suggestion to be made that it is truly a sensitization disease. Some observers have also placed it among the endocrine disturbances as a point of departure in their studies. That migraine and epilepsy are transmitted from generation to generation as an expression of the same underlying

replace the migraine attacks as age advances Schumacher and Wolff's (1941) interesting studies indicated the possibility that the preheadache prodromata follow occlusive vasoconstriction of cerebral arteries whereas the headache itself results from dilation and distention chiefly of branches of the external carotid arteries. The finding of focal electroencephalographic changes during the scotomas of migraine, by Engel *et al.* (1945), are consistent with these findings of Schumacher and Wolff. The observations of Redisch and Pelzer (1944) during migraine attacks induced by forced water ingestion indicated to them a definite relationship between the fluid balance of the

differentiated from headache occurring in hypertension and in nephritis with retention, also from the toxic headache of excessive alcohol and tobacco indulgence, the headache of eyestrain and of nasal sinusitis, the bandlike headache that occurs in some of the psychoneuroses, the headache associated with arthritis of the cervical spine, the headache caused by intracranial lesions and by syphilis. The headache differentiated by Horton as histaminic cephalalgia is felt by Keeney (1946) not really to be a distinctive entity.

Alvarez (1947) says that the headache is only one of the migrainous person's troubles and that one should learn to recognize a migrainous personality and constitution, the outstanding characteristics of which are that the individual is hypersensitive quick of thought and movement, has a tendency to grow tense, to worry, to tire easily, and to sleep poorly. Usually also he, or more often she, is a perfectionist who works fast and accurately and likes to push other persons along to work fast with him; anything out of the ordinary is likely to be upsetting, and naturally such persons like to avoid bustle and noise, bright lights and crowds and "functions." Migrainous persons are often ones who have considerable to be concerned about, because they are the type upon which the world unloads its burdens and worries, for they are the ones who can assume responsibility and bear it conscientiously. However, a good many migrainous individuals have days on which they feel only "half alive." Alvarez would bring allergy, hypertension, dysmenorrhea or psychopathic disorders into the picture only as additional things that are superimposed upon the migraine. He admits that a high proportion of migrainous persons are markedly allergic but feels that their sensitivity to various allergens is just a part of their exaggerated sensitivity to all stimuli.

THERAPY

Psychotherapy.—Friedman *et al.* (1946), in reviewing their experience with all of the various drug measures currently employed, concluded that for best results in most cases such psychotherapy as lies within the province of the [illegible] is as important as drug therapy. Surely if Alvarez' (1947)

ed above, is valid, then the non-special-

an important therapeutic approach to

the disease, for these people with the migrainous constitution and personality probably very frequently have their attacks initiated by things which, once having had the true nature of their ailment brought to their attention, they could

learn to av[illegible] Indeed [illegible]
from their [illegible]
tenor of th[illegible]
eating of meals, the freer they remain from attacks, some, indeed, are even able to state with positiveness that a certain type of emotional or even physical indulgence will invariably induce the headache. Perhaps it should be the principal duty of the physician treating migraine to seek to expose such "trigger mechanisms" in the lives of all his patients.

Rest, Analgesics and Sedatives.—Rest in bed is nearly always self-imposed by the worst sufferers from this disease, since it markedly lessens the throbbing of the head and of course decreases the bodily movements that so often give rise to added quirks of pain. Darkening of the room and the use of cold compresses are also helpful measures. In mild cases, any of the sedative drugs (for a list and dosage, see Insomnia) may be employed, phenobarbital being latterly preferred In severe attacks prohibitive doses would have to be used in order to bring about any reduction in the suffering. Better results follow the use of the analgesics in mild cases, though their effectiveness seems to be much greater when the attack is beginning to wear off than when it is at its height. Aspirin (acetylsalicylic acid), in a dose of 5 to 15 grains (0 3–1 gm) at intervals of three hours for 4 or 5 doses is often used, but it sometimes serves only to make the patient more uncomfortable by reason of the perspiring induced. A capsule of pyramidon (amidopyrine) and caffeine citrate, 5 grains (0 3 gm.) of the former and 2 grains (0.13 gm.) of the latter, three or four times during the twenty-four hours, is effective in some cases; but one should be definitely aware c[illegible]
—personally, I feel [illegible]
(0 3 gm) of phenace[illegible]
may also prove effective, especially when combined with caffeine as above, if used several times at three-hour intervals, larger doses are seldom more effective and are more likely to cause the undesirable side-effects of this group: sweating and chills, gastric disturbances, skin eruptions, renal irritation, methemoglobin cyanosis and collapse. In some cases, codeine sulfate in a single daily [illegible]
[illegible]
[illegible]
a [illegible]
connection with the opiates, need not be feared from the use of codeine. Morphine, dilaudid and demerol are, of course, absolutely contraindicated.

Ergotamine Tartrate (Gynergen).—The work with ergotamine began on the Continent but a number of American reports are now available; the best of these for presentation here is still probably that of O'Sullivan (1936), who with her associates made a careful study of the drug's effects at Bellevue Hospital. The following are the significant points. (a) All but eight of the ninety-seven patients were benefitted in the sense of having obtained great relief from [illegible]
que[illegible]
reli[illegible]
dru[illegible]
dos[illegible]
time. (d) If the patient takes the drug as soon as she is sure that an attack is on the way the dosage required to check the attack is much smaller than if she

delays. (e) The time required for effective control varies from fifteen minutes to five hours. (f) The drug is preferably given subcutaneously in a trial dose of 0.25 mg.; if the control has not been perfect after two or three hours, the dose is repeated, or it is repeated if the attack returns after eight to twelve hours. In those instances in which repetition is necessary, 0.5 mg. is given initially in subsequent attacks; more than this in any attack is rarely needed, 0.75 mg. having been used only three times. (g) It is most important that the patient lie down for one or two hours after medication, not only to assist it but also to diminish the symptoms of overaction of the drug, which occur in many individuals: nausea, vomiting, muscle pains and weakness of the legs, stiffness of joints, a sense of constriction in the throat, and of heaviness in the [illegible]

muscle pains. (h) Response to oral administration of the drug in tablet form is much less satisfactory; if nausea and vomiting have already set in it is useless. Five of the 1-mg. tablets have been necessary at one time to check an attack even before the appearance of gastro-intestinal symptoms; with such heroic dosage, no more of the drug should be given for twelve to twenty-four hours. (i) Use of ergotamine between attacks in the attempt to prevent their recurrence is felt to be unwarranted in view of the very irregular spacing of the attacks; such a practice is also very expensive and possibly dangerous

Palmer (1945) said that in his experience only about 0.25 per cent of constant users of ergotamine exhibit peripheral vascular disturbances and that he has encountered a number of patients who have used the drug recklessly in high dosage almost daily for more than a year without getting into trouble; others, however, have the warning signs develop quickly after use of only a half-dozen doses. He also said that one of the unexpected and unwelcome complications of the use of ergotamine in his experience has been the aggravation or the increase in frequency of the headache.

Dihydroergotamine.—Horton *et al.* (1945) reported on the treatment of seventy-nine patients with typical migraine, and forty-one patients with [illegible] diagnostic features absent), with [illegible]

plete relief in one to four hours, and good that the duration and severity of the attack were markedly reduced I gained the impression from the report of these observers that they felt this drug to be just as good and certainly less toxic than ergotamine. Only 7 per cent of the 120 patients experienced toxic reactions consisting in nausea and vomiting, general malaise, and in one instance pain in the leg. Hartman (1945), Friedman *et al.* (1946), and Clein [illegible] of dihydroergotamine in [illegible] however, there [illegible] e of the agent. [illegible] 45 given intra- [illegible] 1 cc. was probably the average dose used in the studies. One cc of the ampule solution contains 1/60 grain (1 mg.) of the drug; the injection may apparently be given [illegible] intravenously [illegible]

[illegible] f octin hydrochloride [illegible] in eighteen patients.

They found that a few individuals respond to the drug with a hypertension developing within ten to thirty minutes after the injection and persisting for several hours, this hypertension even following the test dose of only 50 to 75 mg. Approximately half of the patients achieved prompt and dramatic relief of the pain, but some of them who used the drug frequently developed nervous tension and palpitation that required sedatives for their control; sometimes the larger doses also caused dizziness and even syncope. MacNeal and Davis concluded that for those patients who can take octin, *i.e.*, those in whom it does not produce hypertensive effects, its superiority over the other drugs employed for symptomatic relief is considerable since it does not produce nausea and vomiting or peripheral vasoconstriction. Palmer (1945) wrote of the trial of octin mucate, 2 grains (0.13 gm.) orally two or three times daily over a period of weeks or months, with an additional intramuscular injection of 100 mg. (1½ grains) of the hydrochloride salt when a headache threatens, this dose to be repeated in two hours if the headache has not been aborted or materially diminished. Palmer (1945) said that results in his twenty-seven cases had been "encouraging." However, Friedman *et al.* (1946) used octin in five patients; four did not experience relief and the improvement in the fifth patient was probably merely coincidental because it was easily ascribable to other circumstances at the time.

Niacin (Nicotinic Acid).—This agent is being used by Atkinson (1944) and a few others as in Ménière's disease (*q.v.*)

Food Elimination.—Keeney (1946) said he felt he could speak for most allergists in saying that one rarely finds an individual in whom it is possible to accomplish anything by elimination of food from the diet; he had no doub

does

him

Histamine Desensitization.—It seems to me that those who attempt to treat migraine through desensitizing the patient to histamine do not understand the fundamental principles of allergy. (See the chapter on Allergy.)

IDIOPATHIC EPILEPSY

(*Paroxysmal Cerebral Dysrhythmia*)

Idiopathic or essential epilepsy is a disease characterized by certain peculiar types of seizure unassociated with characteristic physical signs or demonstrable pathologic lesions. In the majority of instances the onset of the attack occurs before the twentieth year, in more than half before the fifteenth, and perhaps in average cases between the third and eighth year. In some instances the imminence of a convulsion is heralded by a warning visual, auditory, or other type of fleeting aura, which is followed in about 50 per cent of cases by the sinister epileptic outcry; then follow the sudden loss of consciousness, the defenseless fall, the moment of pallor, cessation of respiration and general muscular rigidity of the decerebrate type. Transition

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the pulse is rapid and feeble, the deep reflexes are greatly diminished, the

blood pressure is low, the pupils are first constricted and then dilated and usually immobile to light, foam appears on the lips, bestial sounds are made and the urine or feces may be violently ejected. Following the subsidence of this stage, the patient passes into a deep stupor of several hours, though in some instances this stuporous state is not marked or the patient may partially regain consciousness for a few moments and then fall into a more natural type of deep sleep. For a considerable time after awakening, the state is either one of dreaminess, irritability, delirium, or mania during which acts of great violence may be committed. This is the classic *grand mal* seizure. In severely afflicted individuals the attacks occur with sufficient frequency to mar the pattern of life, but in rare instances only one or two or three attacks, with many years between, are experienced by an epileptic throughout a long lifetime. The *petit mal* attack consists in only a momentary loss of consciousness, or some other sort of flashing sensory disturbance, without the occurrence of a full convulsion and its sequelae; but in petit mal there may occur rhythmic movements of the eyelids or of the head, or there may occur single shock-like (myoclonic) jerks of the arms or trunk muscles without apparent loss of consciousness, and there may also be a sudden collapse of muscles with resultant nodding of the head or perhaps even a fall; involuntary micturition sometimes occurs also. And then there are the cases in which so-called *equivalents* replace a typical convulsive seizure: unexplained outbursts of temper, tantrums, periods of amnesia, sudden irrational and destructive activity, attacks of paroxysmal abdominal pain, periods of dulness and [illegible] bizarre equiv- [illegible] ypes, according [illegible] te of affairs in which one convulsion succeeds another so rapidly that the patient practically never recovers consciousness; he presents all the signs of profound intoxication and usually dies from heart failure or pulmonary edema

Epilepsy was recognized as an entity in very ancient times. Sudhoff interpreted the concept *bennu*, in the tablets of King Assurbanipal of Assyria (668–626 B.C.), as epilepsy, and the description of the grand mal type of the disease written by Hippocrates (460–370 B.C.) would almost suffice for any present-day textbook. In the Middle Ages it was customary to include epilepsy with the diseases then recognized to be contagious—bubonic plague, tuberculosis, anthrax, scabies, erysipelas, trachoma and leprosy—and to ban the afflicted from the cities, or at least not to permit them to sell food and drink. At the present time we are convinced that the disease is not infectious, and certain that the epileptic predisposition is inherited; Lennox (1945) said that among the near relatives of unselected epileptics, both epilepsy and cerebral dysrhythmia occur approximately five times more frequently than in the general population Otherwise the etiology of the disease remains unknown. The most significant advance that has been made in all the long history of epilepsy is the recent recognition, largely as a result of the studies of Gibbs and his associates at Harvard, that in about 95 per cent of patients there are abnormalities in the electroencephalogram that show up even during an asymptomatic period; this is the evidence, indicating that seizures are accompanied by profound alterations in the rate and force of the electrical pulsations of the cortex, that warrants us in applying to epilepsy the new title "paroxysmal cerebral dysrhythmia." It has been conservatively estimated that 500,000 individuals in the United States have epilepsy.

THERAPY

If essential epilepsy is incurable, and it probably is in the present state of our knowledge, nevertheless very much can be done for these individuals. But the physician who merely writes a prescription for one of the anticonvulsant drugs, makes a few vague remarks as to dietary restrictions, suggests that the family make life easy for the patient, and then takes no vigorous

Schooling and Employment.—Paskind and Brown (1943) expressed the feeling that eventual mental deterioration in epilepsy is taken entirely too much for granted in all cases merely because it frequently occurs in advanced committeed cases, and they thought that the disorder is definitely of two types: one in which mental deterioration occurs and the other in which it does not. Lennox (1945) said that fortunately, contrary to common lay and medical opinion, serious mental deterioration is unusual; of 1905 private and clinic patients whose records were personally examined, 67 per cent were found to be mentally normal, 23 per cent slightly deteriorated, and only 10 per cent definitely deteriorated He said that the proportion of mentally normal epileptics decreases somewhat with the passage of years and with the total number

cipally in such traits as egotism, rigidity, moodiness, perseveration (persistence of one reply or one idea in response to various questions), but that such traits are rarely manifested in mentally normal patients who have received intelligent treatment. It is Peterman's (1945) opinion that the epileptic child in

students graduated or were continuing their courses with promise, the gradu-

acid and the lactic acid that result from muscular and mental work are as important as drugs in the inhibition of seizures and that not stagnation but productive activity is the pass-word to a life with fewer seizures and more

attention. It is a fortunate thing that as the patient grows older the seizures

helpful to obtain some of the free literature from the National Association to Control Epilepsy at 22 East 67th Street, New York City.

Marriage.—About half of the near relatives of epileptics have disturbed brain rhythms and in about 90 per cent of families one or both parents of an epileptic have some degree of dysrhythmia. Lennox (1945) therefore says that if an epileptic, or a non-epileptic who has cortical dysrhythmia, marries he should choose a person whose brain waves are normal, thereby greatly reducing the existing chance (about one in forty as against one in 200 for the non-epileptic population) that any given child will be epileptic.

Phenobarbital (Barbitone).—Butter (1945), in analyzing the treatment of 375 cases treated in an institution for the epileptic, found that phenobarbital alone or in combination with other drugs was the most useful agent in 74.1 per cent of the cases. Peterman (1947) said that it remains the drug of choice in the treatment of grand mal in children. The latter observer placed adequate dosage at about ¼ grain (15 mg.) two or three times a day for a child under two years of age, ½ grain (30 mg.) at the same intervals from two to six years, 1 grain (60 mg.) from six to ten years of age, and 1½ grains (100 mg.) from ten to fifteen years of age. In resistant cases in adults, 2½ grains (0.2 gm.) may be given three or rarely four times daily for a limited period, but many adults ... 2 grains (0.1 or 0.12 gm.) daily. The ½ grain tablets

3 grains (0.2 gm.) of the drug. The dose of phenobarbital sodium is ...

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should always be borne in mind as possibilities, since they probably occur as often following small as large doses: (a) a dermatitis resembling that of measles or scarlet fever, though it is usually very itchy (a few cases of fatal exfoliative dermatitis are on record); Peterman (1931) reported an eruption exactly simulating bromoderma which followed a healed true bromoderma on the same sites; (b) a peculiar eruption upon the tongue; (c) states of apathy, mental sluggishness and slow speech much resembling those seen as a result of bromide therapy; (d) great muscular weakness; (e) extreme irritability, sometimes leading to violence; (f) a state of intoxication that may be mistaken for acute ... and chronic epigastric pains.

...st petit mal and not at all effective

...Merritt and Putnam, at Harvard, introduced ... ial. The drug, which is diphenylhydantoin sodium, is analogous to the barbiturates in its chemical nature,

being a derivative of glycolyl urea instead of malonyl urea. Lennox (1945) said that dilantin is the drug of choice in grand mal, though if the case is a fresh one and immediate control of the seizure is not essential, phenobarbital is best used first because of the ease of handling and the relative infrequency of side effects. However, Butter (1945), in analyzing the results of drug treatment in 375 cases of institutionalized epileptics, found that dilantin alone or in combination with other drugs had been suitable in only 22 6 per cent of the cases. Peterman informs me that he has found dilantin quite unsatisfactory in children and that almost all of the patients whom he has treated with it have returned to phenobarbital by their own choice because of dilantin's side reactions. As a matter of fact most men find that even in the treatment of adults dilantin is best employed in combination with phenobarbital. Of course [illegible]

daily and increased if necessary in increments of 1½ grains (0.1 gm) every ten days or two weeks until relief is obtained or toxic symptoms appear, in most cases after the control level is reached this must be maintained without reduction. Patients who have relatively infrequent attacks are often more difficult to treat but they are frequently given 6 to 7½ grains (0 4 to 0 5 gm.) daily in the attempt to prevent attacks which might interfere with their occupation or education All observers agree that the change over from phenobarbital to dilantin must be made with extreme caution.

Unfortunately petit mal attacks are often of more frequent occurrence under dilantin; Lennox (1947) found that the drug provoked an increase of seizures of this type in 18 per cent of a large series of cases

It is in the prevention of the psychic equivalent or psychomotor seizures that dilantin is preeminent, and this is a noteworthy fact because none of the other drugs have much influence upon this type of epilepsy.

Dilantin has the great advantage of not acting as a sedative, in fact it is the general impression that many patients are mentally brighter while taking the drug. Ross and Jackson's (1940) exact study of this latter point did not reveal any significant influence on intelligence ratings, but about half their patients showed an improvement in conduct, and performance ratings were raised appreciably in a small percentage; McLendon (1943) found that his institutionalized patients with mental deterioration became more friendly and alert under dilantin and required less supervision than was necessary under phenobarbital. Unfortunately, however, the drug gives rise to quite an array of toxic symptoms of other sorts Pratt (1939) reported toxic reactions in 78 per cent of fifty-two patients, the most frequent in occurrence being subjective tremulousness with a feeling of apprehension and tension, tremors, dizziness, ataxia, nausea and sometimes vomiting, burning sensation in the eyes, diplopia and blurring of vision; psychotic reactions occurred in five cases Williams (1939) found that toxic symptoms arose in 36 per cent of his eighty-three patients, Blair (1940) in 58 per cent of his thirty-six patients, and all of Finkelman and Arieff's (1942) forty-one patients showed some side effects on the nervous system ranging from apprehensiveness and irritability to a paranoid confusional psychosis and encephalopathy. Kimball and Horan (1939) found peculiar hyperplastic reactions in the gums in about half their patients and so have numerous other

observers since; Merritt and Foster (1940), confirming in man earlier findings in animals, established that this gum reaction is not caused by drug-induced vitamin C deficiency, though at times the appearance of the gums does bear some superficial resemblance to the picture seen in scurvy. Less frequently occurring reactions involve the gastro-intestinal tract and the skin (Ritchie and Kolb, 1942, reported a fatal case of hemorrhagic erythema multiforme and there have been a few recorded instances of exfoliative dermatitis); hirsutism in adolescent girls, nosebleed, purpura, cardiovascular disturbances (Finkelman and Arieff, 1942, recorded electrocardiographic evidence of involvement of the heart). McCartan and Carson (1939) reported a slight progressive diminution of the red cell count in all of their twenty patients, a tendency to lowering of the white count due to a fall of granulocytes, and an increase in the number of eosinophils in thirteen of the cases; but Merritt [illegible]

reactions sooner or later. The danger to life from the accidental taking of a large overdose of dilantin seems to be very slight. Aring and Rosenbaum (1941) reported a patient who upon four occasions ingested 60, 90, 105 and 57 grains (4, 6, 6 8 and 3.8 gm.), respectively; the chief symptoms each time were exhilaration, light-headedness, dizziness, nausea and vomiting, headache, staggering diplopia-nystagmus, difficulty in converging the eyes, pupillary abnormalities, ataxia, tremor and changes in reflexes Robinson's (1940) patient, who ingested 67½ grains (4.5 gm.), was in coma for a few hours and then suddenly regained consciousness.

Tridione.—This agent has found a preeminent place in the treatment of petit mal. Lennox (1947) reported that 31 per cent of 166 patients became entirely free of seizures when treated with tridione and that an additional 32 per cent had less than one-fourth the previous number of seizures. Of the patients who were [illegible] half revealed evidence of pathologic condi[illegible] , were obtained in patients less than t[illegible] itients whose petit mal seizures were [illegible] ven phenobarbital, benzedrine or ephedrine in addition to tridione without substantial additional benefit. It was found also that when tridione is omitted, weeks or months may elapse before the attacks of petit mal return; this is quite in contradistinction to phenobarbital, dilantin and the bromides, for when they are abruptly withdrawn the patient usually has a flood of seizures.

Tridione is available in capsules of 5 grains (0.3 gm.). Lennox (1947) said that the beginning dose for infants is 5 grains (0.3 gm.); for children of two to four years, 10 grains (0.6 gm.); for children of five years and above approximately 15 grains (0 9 gm.). This is a total daily dosage in all cases. The usual dose for adults is approximately 15 to 18 grains (0.9 to 1.2 gm.) daily. The daily dosage is usually divided and given with meals; in young children the [illegible] the food. If gastric distress follows [illegible] id should be taken with it. Lennox [illegible] are not controlled the daily dose is increased by 5 grains (0.3 gm.); this is repeated at monthly intervals until therapeutic relief is secured, toxic symptoms appear, or double the initial dose is being taken. Maximum improvement usually occurs in one to four weeks. If the seizures have been absent for three months, and the electro-

encephalogram is free of dart and dome formations, the dosage of the drug may be reduced by one capsule every two months until none is taken or seizures return.

Lennox (1947) said that in his experience tridione has acted more as a convulsant than as an anticonvulsant in cases of grand mal epilepsy, and he was therefore very definitely of the opinion that it should not be used when the grand mal occurs alone; however, when petit mal seizures are complicated by grand mal, as they were in 55 per cent of the patients in his series, and the grand mal seizures recur more often than yearly, it was his feeling that both tridione and an anticonvulsant, either phenobarbital or dilantin or one of the newer drugs, should be tried. Lennox felt that his experience of the drug in psychomotor seizures was too limited to justify definite conclusions but that tentatively he could say that when used alone it is ineffective though an occasional patient will benefit from a combination of tridione and dilantin. DeJong (1946), however, reported good control of psychomotor attacks with tridione used in various combinations with dilantin, or with dilantin and phenobarbital.

Among the 222 patients treated with tridione for petit mal who reported adequately, Lennox (1947) said that 122 had some sort of untoward reaction. The largest proportion of these (31 per cent) reported some degree of photophobia when going from indoors into the brightly lighted outdoors; in the most severe cases patients were required to wear dark glasses when outdoors, and some individuals complained of associated pain in the eyeballs and one of difficulty in focusing the gaze. Mackay and Gottstein (1946) commonly observed photophobia in adolescents and adults but very rarely in children, and it was not very troublesome. In Lennox' experience simultaneous ad- [illegible] pleasant side effects in order of their frequency in these 222 patients was the [illegible] bleed, 3 each; sleepiness, double vision and poor circulation, 2 each; sneezing, hiccup, and aplastic anemia, 1 each. One adult who by mistake took a very large daily dose for a month experienced mild confusion that cleared when the dosage was reduced. None of the patients developed symptoms of psychosis, hypertrophy of the gums or ataxia, though Lennox said that it had been reported to him that gross ataxia had been seen in several epileptics whose brains had been severely traumatized in the war. He said that opposed to the nine patients with difficult behavior were twenty in whom the behavior was greatly improved, and that against the two with decreased alertness were fifteen who became more alert.

In Lennox's (1947) series of 127 patients taking tridione in whom repeated monthly examinations were made for from several months to two years, none had a significant decrease of hemoglobin, red cells or platelets, but in 6 per

cent of the cases the neutrophilic granulocytes decreased to 1600 or less per cc.; tridione medication was discontinued in these cases. Also in one-fourth of the patients the eosinophils increased to from 6 to 25 per cent. To this record, however, there should be added one case of aplastic anemia subsequently treated and reported upon by Harrison *et al.* (1946), the patient being a girl of sixteen years who developed the fatal reaction after having taken tridione and a drug of the dilantin series, methylphenylethylhydantoin, concurrently for a period of six months. A study of the bone marrow at autopsy indicated that about one-fourth the normal amount of hematopoietic tissue was present. The patient had bled profusely. Mackay and Gottstein (1946) reported the case of a twenty-four-year old patient who, after ten months' treatment on tridione in combination with phenobarbital, developed acute aplastic anemia, [illegible] and then [illegible] and died, the autopsy revealing exten- [illegible]

in the bone marrow but an actual destruction of them in the peripheral blood stream. Lennox (1947) said he had heard of another death from aplastic anemia in addition to the two discussed above, and he had also learned of three cases of toxic amblyopia that cleared when medication was stopped.

In a summarizing opinion of the toxicity of tridione, Lennox (1947) said that less than 10 per cent of his group of epileptics had to stop the medication because of toxic complications, though medication had been stopped in six patients who were free of seizures as attest to the permanency of the arrest of their disease.

The Bromides.—The bromide salts were introduced into the treatment of epilepsy in 1858 and enjoyed an undisturbed and deserved preference over all other remedies until their position was challenged by phenobarbital and more recently by the newer drugs. Bromides have now been almost abandoned but it is well to bear in mind that this was not because they were not effective but because they purchased their often very excellent anticonvulsive effect at the price of sluggishness and apathy, skin rashes and gastric disturbances. Also, as in the case of phenobarbital, grand mal was much more effectively treated than petit mal and the psychomotor attacks were not affected at all. Average adult bromide dosage is 15 grains [illegible] study is required to determine, by adju[illegible] amount required in a given case. [illegible] proportion to their weight. Bromide therapy is more effective if the diet is kept relatively salt-free, but resort to this measure is usually necessary only in very resistant cases.

The following prescription is acceptable for disguising the bromide taste.

℞	*Sodium bromide*	℥i	30 0
	[illegible]	℥i	30.0
	[illegible]	℥iv	120 0
	[illegible] daily.		
	[illegible] bromide.)		

Bromide overdosage is combated by stopping the administration of the bromide, by pushing fluids, and giving sodium chloride. Sensenbach (1944) stated that the giving of 6 to 8 gm. of sodium chloride daily appears to be optimum dosage, but he warned that the response to therapy is slow and rarely dramatic

said that average dosage for a child is 0 4 gm. and that average dosage for the seventy-eight youths and adults in his series was 0.6 gm. daily, though the individual variations were from 0.3 gm. to 1.0 gm. Rash appeared in about 10

trolled by dilantin.

tried caffeine and obtained no beneficial effect.

The Ketogenic Diet.—The rationale of this diet is believed to lie in its

by what Horder (1934) aptly described as "appreciation of the fact that certain noises are needless and preventable." The trick here—and I shall not seek to make Horder responsible for the remedy, of which indeed he may not approve—is to assure these people that there is ample ground for their peevishness, and that most impressive (one need not add rather hopelessly ineffectual) bodies of citizens are "dealing" with the matter in several countries, but that *pending the arrival of blessed silence* the only sensible thing to do is shut out the horrible jangle—then follows the advice to visit a sport- [illegible]

but they quickly grow soiled and easily lose themselves A black sock, fastened toe to top with a very small safety-pin, fits well over the head and is not excessively warm.

Diet.—Many individuals cannot sleep if they have recently eaten, therefore nearly all people think that late supper-eating is harmful. This is of course not based on fact, and some insomniacs will be actually relaxed by a bit of food taken just before going to bed. Actually, in just this last group especially, in rare instances blood sugar studies will reveal the insomnia as one of the manifestations of hyperinsulinism, dealt with elsewhere in the book. In an interesting study, Miller (1945) treated twenty patients suffering from insomnia and tension states by means of a salt-restricted dietary regimen with the result that all save three obtained pronounced or moderate relief from tension and sleeplessness; controls on thirteen patients revealed that ten suffered relapses following the addition of salt to the diet. It was said that improvement was noted generally in the duration and regularity of sleep with a concurrent reduction in lability and intensity of emotional response on the lower salt intake For a low sodium diet see Index.

Barbiturates.—Of the host of barbiturates it seems to me that the practitioner needs only the following for action in the categories indicated *Seconal* is a very rapidly acting barbiturate given in average adult dose of 1½ to 3 grains (0 1-0.2 gm.), its action is not sufficiently prolonged to be satisfactory in the patient whose difficulty is in remaining asleep, but it certainly will not make him loggy next day. *Amytal* does not act so rapidly but its action is somewhat more prolonged; it is given in average dosage of 1½ to 5 grains (0.1-0.3 gm.) *Pentobarbital (nembutal)* has a rapidity and duration of action somewhat like that of amytal; it is given in an average dose of 1½ grains (0.1 gm.). These two drugs are having considerable and well deserved vogue nowadays; they put the patient to sleep reasonably quickly (half an hour or so), hold him there long enough, and deliver him to the [illegible] *Phenobarbital* is the slowest acting of the lot but its [illegible] to 3 grains (0.1-0.2 gm.). [illegible] or *capsules* because their soluble sodium salts break down too rapidly to enable them to be safely prescribed in bottle form. In many instances these barbiturates can be more effectively employed as sedatives than as hypnotics, *i e*, the hypnotic dose [illegible] is divided into th[illegible] day such as after [illegible] larly well employe[illegible] nervous jittery state Barbiturate ingestion occasionally causes skin [illegible] tions and vague aches and pains about the body, and not infrequently habitu-

ation of an insidious and serious type is induced. Osgood (1947) reported nine cases of convulsions resulting from the withdrawal of several members of the barbiturate series. In two instances the withdrawal was abrupt, but in the other cases the convulsions occurred after the drug had been only partially reduced.

The Chloral Group.—Though possessing the advantage of being sufficiently soluble to prescribe in solution, *chloral hydrate* is objectionable in taste and very irritating to the stomach; it is a cardiac depressant only in much larger than ordinary doses Twenty to 30 grains (1 2–2 gm) usually induce sleep within thirty minutes (occasionally brief excitement precedes sleep; very rarely the drug's only action is excitatory) but do not maintain it more than a few hours. The peripheral vessels being somewhat dilated by this dose (reflecting action on the vasomotor centers), the patient should be well covered if in a cool or breezy room. Residual symptoms on the following day are quite infrequent with chloral nor is it truly habit-forming, but insomniacs tend to hold on to [illegible]

second is acid sweet; neither disguises chloral very well but this cannot be helped As a matter of fact, I think that too pleasant hypnotics such as the barbiturates now in vogue are a habit-inducing curse.

℞ [illegible]	ʒi	30 0
[illegible]	ʒii	60 0
[illegible]	ʒiv	120 0

[illegible]

℞ Chloral hydrate	ʒi	30 0
Syrup citric acid	ʒi	30 0
Water to make	ʒiv	120 0
Label Same		

Until recently it has been held that the addition of alcohol to prescriptions containing chloral hydrate promotes the formation of chloral alcoholate (especially [illegible]

n [illegible]

([illegible]

c [illegible]

considerable amounts of alcohol out of chloral-containing prescriptions.

Fantus (1936) recommended the following dosage of chloral hydrate for children, to be given in starch water as a retention enema one to two months, 1¼ to 2¼ grains (0.1–0.15 gm.), one to two years, 8 to 12 grains (0 5–0.8 gm.), six years, 15 grains (1 gm.), ten to fourteen years, 25 to 30 grains (1.5–2 gm.). [illegible]

wi [illegible]

aci [illegible]

Benedict's solution).

Attempts to modify chloral under the mistaken idea that ordinary therapeutic doses are dangerously depressing to the circulatory apparatus have only served to weaken its hypnotic action; a possible exception is *butyl chloral hydrate*, which is given in capsules, 5 to 20 grains (0 3–1.2 gm.), and is said to be of some value if the sleeplessness is caused by pain, as chloral hydrate certainly is not. Modification away from the gastric irritation has been more successful, and in *chlorbutanol* (*chloretone*) we have a product that is not only hypnotic but actually locally anesthetic, though very much milder

than the cocaines and usually employed only as a dusting powder. Given internally, 5 to 20 grains (0.3–1.2 gm.) in capsules or tablets, it slightly anesthetizes the gastric mucosa; it is therefore used as a sedative in vomiting and in attempting to prevent seasickness. I think the profession would do well to use this drug more often in insomnia, since it affords chloral hypnosis without gastric irritation.

Paraldehyde.—This agent is much employed to calm individuals in a state [illegible]

danger of inducing the habit of tippling must always be borne in mind.

Bromides.—The bromides are not primarily hypnotics; however, they are often of value in one of two ways in aiding the patient to sleep: (a) in small doses of 5 to 10 grains (0.3–0.6 gm.) three times daily their sedative action overcomes the hyperexcitability responsible for sleeplessness in some cases; (b) given in a single dose on retiring (10–20 grains) in combination with a reduced dose of chloral they often prolong the sleep initiated by the latter drug. However, Gold (1944) well pointed out that if the patient takes a mixture of this sort for a long period of time, he will after a while develop a relatively high bromide level because he excretes the chloral much more rapidly than he does the bromide. Gastric irritation, bromoderma and the other [illegible] but one

[illegible] ple inor-

[illegible] l having

some bromine attached Either of them in a dose of 5 grains (0.3 gm.) three or four times daily, or 10 to 20 grains (0.6–1.2 gm.) an hour before retiring, is of value in the type of insomnia in which sedatives rather than stronger hypnotics are indicated Bromoderma is apparently of very rare occurrence and habit-formation comparable to that with the barbiturates has not been reported. These drugs are insoluble and must be prescribed in capsules or tablets When they maintain sleep for only a few hours it is permissible to give [illegible]

supply so and so many of a proprietary tablet or capsule containing these drugs in combination. Most of these preparations contain amidopyrine, which it seems to me we are no longer justified in using in this loose way—see Agranulocytosis Furthermore, it is very bad practice to do no more for the patient than advise that he buy another little tin box or glass bottle full of the tablets he knows so well The following is the sort of prescription I have in mind; it contains 3 grains (0.2 gm.) of acetanilid and $\frac{3}{4}$ grain (0.045 gm.) of seconal per capsule:

℞ Acetanilid	gr xxxvi	2.4
Seconal sodium	gr ix	0.54

Make 12 capsules
Label· 1 capsule as directed

Acetphenetidin (phenacetin), or acetylsalicylic acid (aspirin), either in the amount of 1 drachm (4.0 gm.), so that each capsule would contain 5 grains, might equally well have been used instead of the acetanilid. Indeed, aspirin

in tablets is not known as a hypnotic and the patient will scorn suggestion of its use for that purpose.

DELIRIUM TREMENS

This is a type of acute insanity that develops in a relatively large propor-

drawal of liquor, these last cases being of extremely rare occurrence After one or more days of prodromal uneasiness and insomnia, the patient begins to tremble and becomes actively delirious in which state he remains without sleep for an average period of five or six days and then slowly recovers or dies; 9 per cent of the 305 patients of Rosenbaum *et al* (1941) had convulsions. The outstanding features of the delirium in typical cases are: first, the fact that the patient is aware of his own personality but is disoriented as to time and the outside world; second, that he is in a state of great fear, and third, that the hallucinations are of sight almost exclusively. The temperature remains normal in uncomplicated cases unless muscular activity is very great; the heart rate and force also correspond directly to the patient's activity except insofar as they are altered by previously existing cardiovascular disease. Delirium is usually superseded by heavy sleep of several days' duration. In severe cases the state of postdelirium stupor known as "wet brain" super-

reported at about 15 per cent, but in some clinics specializing in the treatment of this condition it is much lower: for example, Rosenbaum *et al.* (1940), at the Cincinnati General Hospital, reported 534 cases with a gross mortality of 2.5 per cent and a net mortality, after omission of complicated cases, of 1.7 per cent.

THERAPY

There is so much confusion and contradiction in the therapy of delirium tremens today that it seems to me most advisable not to attempt a review of the literature here but rather to state in simple terms the treatment regimen employed at Bellevue Hospital, as reported by Wortis (1940). Thereafter a bit more will be said regarding sedation.

A General Plan of Treatment.—(a) Withdraw alcohol abruptly. (b) Give sedative medication judiciously, paraldehyde being preferred, and morphine being condemned. (c) Omit restraint unless absolutely necessary. (d) Give carbohydrate in large quantities. (e) Administer sodium chloride in an attempt

both to combat dehydration and to restore the normal acid-base equilibrium of the body. (f) Provide a high-calorie, [illegible] Do lumbar punctures for diagnostic p[illegible] *precipitating factors with specific therap*[illegible] according to the needs of the patient.

Sedation.—The ordinary hypnotic drugs (see Insomnia) in any dosage likely to be safe are practically worthless, paraldehyde being the exception. This drug is similar to but more rapid in its action than chloral hydrate; unfortunately it may occasionally contribute to the excitement. It is a colorless liquid with odor and taste so disagreeable as very much to limit its use, and also it is more irritant to the gastric mucosa than chloral hydrate. Administration sometimes causes coughing, and the odor persists in the breath for a long time because the drug is partially excreted through the lungs (though principally in the urine). It is certainly less toxic than chloral in large doses, but it is prone to cause habituation despite its taste. Ordinary dosage is ½ to 2 drachms (2–8 cc.) on crushed ice or in highly alcoholic vehicle, such as the tincture of sweet orange peel. The following is about the best that can be done, but it is none too good; perhaps diluting with sweetened iced tea instead of water, as Fantus suggested, may be worth while

℞	Paraldehyde.	℥ij	60 0
	Tincture sweet orange peel to make.	℥iv	120 0
	Label 1 to 4 teaspoonfuls well diluted upon retiring		

[illegible]

with doses of 8 to 12 cc. every hour, control of the case usually being obtained, if other measures are adequate, in two or three hours. Paraldehyde may also be given by rectum, diluting the dose well with water and giving as a retention enema. It is also sometimes given intravenously in 1 cc. dosage to obtain its full anticonvulsant action. Pentothal solution is also occasionally employed intravenously in small dosage, but of course all intravenous medication is extremely difficult in these wild patients. Morphine is nowadays considered dangerous to use because of its alleged ability to increase intracranial pressure. A number of workers in recent years have employed insulin in order to calm the patient in the treatment of delirium tremens; the latest of these reports to come to my attention is that of Tillim (1944), according to whom the best results are obtained when the patient is given an average of forty to eighty units of insulin, after which he becomes soporose and perspires freely. If the initial dose is not sufficient to quiet him in an hour, it is said that a second injection may be given intravenously; then if he shows signs of becoming too deeply depressed, dextrose may be given in fractional doses intravenously, or 6 to 8 ounces of sweetened fruit juice may be given by mouth. The patient should be supplied with plenty of water to drink throughout the treatment and after it may be permitted to take a large meal, for which he will probably have an excellent appetite. It is said that one to four such treatments (two seem to be permissible within a single twenty-four hour span) will suffice for recovery and a considerable reduction in the length of the hospital stay.

SEASICKNESS AND AIRSICKNESS

There are some individuals who suffer from loss of appetite and low-grade nausea, but not actual vomiting, throughout the first few days of a sea voyage and then recover their normal feeling of well-being; others there are who experience only an excruciating headache without the least gastro-intestinal symptoms; but the symptoms in the most frequent type of the malady consist in discomfort in the epigastrium, anorexia, salivation, headache, dizziness, weakness, cold perspiration, greenish pallor, great dejection and bouts of vomiting with or without nausea Most cases terminate spontaneously after a few days at sea, but there are individuals who suffer continuously throughout an entire voyage; according to Schwab (1943), sailors in War II sometimes developed definite psychoneurosis as a result of prolonged bouts of seasickness. Even professionals with many years of seafaring experience are occasionally made slightly ill when the ship begins to pitch or roll in an unusual fashion, particularly if they walk to a part of the vessel they are not in the habit of visiting.

In airsickness the comparable bout of nausea and vomiting with all the accompaniments may be just as severe as in seasickness, but under the conditions of ordinary civilian air travel the attack at most does not last more than a few hours.

From their experimental studies during War II in animals and man, Morton *et al.* (1947) felt it probable that the most important factor in motion sickness is stimulation of the utricles by linear accelerations in the vertical plane of the head, *i e*, vertical acceleration and deceleration in the long axis of the body with the head erect. Other beliefs, none of which can as yet be entirely discarded, are the following. (a) that confusion results from the multiplicity of unusual stimuli coming along those sensory nerves that ordinarily have to do with the adjustment of our bodies in space, (b) that there is excessive discharge along either parasympathetic or sympathetic pathways depending upon whether the individual is "vagotonic" or "sympatheticotonic", (c) that eyestrain caused by the glare of the sea and sky, and the unusual fixation upon moving objects, reflexly causes the symptoms, (d) that the wide excursions made by the freely movable organs of the abdominal cavity unduly irritate the vagus nerve; (e) that autosuggestion is causative, (f) that the malady is an acidosis.

THERAPY

[illegible]

assigned to him, use a vomit bag, and hope that his fellow passengers are not too much annoyed by his loud goings-on

Value of Fresh Air.—The seasick patient should recline on deck, if possible; however, many patients are embarrassed by their illness in the presence of others and can relax freely only in the privacy of their cabins, in which cases all facilities for maintaining the circulation of the air in the room must be

utilized. In the air, the patient usually is able to control the ventilation over his own seat and probably does well to maintain a considerable stream of fresh air coming in upon him.

Prevention of Eyestrain.—The seasick individual should face the deck-house and not the sea and should avoid using the eyes as much as possible, reading only for brief periods and keeping the eyes closed at other times. Some persons immure themselves in a darkened cabin as soon as they board ship and leave it only when the port of destination has been reached. Perhaps a few thus avoid illness, but the fact should not be overlooked that blind persons also suffer from seasickness. I once watched a fellow air passenger who kept his eyes squeezed closed almost with the passion of a compulsion neurotic but who nevertheless gagged and vomited (not always too accurately!) throughout the four hours of the journey.

Plugging of the Ears.—The simple procedure of plugging the ears with cotton is said to relieve the symptoms of seasickness in some instances; what is put on the cotton is of course of no importance—indeed, I think the sole effect is psychic.

Abdominal Binder.—The use of a tight binder across the lower abdomen has many staunch supporters among experienced travelers at sea; most physicians believe that only those with visceroptosis are thus relieved. However, during my own brief experience as a ship surgeon one of my fellow officers repeatedly demonstrated to me that he became quite ill without his binder in a heavy sea. For all I know this man may have been visceroptotic but I do not believe that he was under any psychic thraldom to his belt, for he had followed the sea for many years and had only recently discovered that he could pass unscathed through storms in this way. I have seen no account of the use of an abdominal binder in the prevention of airsickness.

Diet at Sea.—On this head Orie [illegible] "[illegible] if passengers can be persuaded to eat plenty c[illegible] *that they are never violently sick* [illegible] of course, leads to an early exhaustion of the glycogen reserve. Acidosis is the inevitable sequel. Once this train of events is in progress other factors, such as inability to take food and constant vomiting, tend to make the acidosis more severe." Seasick persons should eat, *no matter if they lose one meal after another*, for vomiting something is easier than the endless retching of an empty stomach. Swallowing small chunks of ice, or sipping cold ginger ale or champagne, is often a helpful measure in dispelling nausea.

Certainly the excessive smoking and drinking in which many individuals indulge while at sea cannot but aggravate the bout of illness when heavy weather comes.

The following carminative mixture will hasten the passage of the stomach contents into the duodenum, and may prevent the *onset of the complete* syndrome in an individual who is only slightly nauseated:

℞	Tincture of capsicum	ʒss	2 0
	Spirits of peppermint	ʒij	8 0
	Tincture of ginger	℥ij	60 0
	Alcohol to make	℥iv	120 0

Label. 1 teaspoonful well diluted after meals, may be repeated if desired

Dextrose.—The suggestion that seasickness is an acidosis *entirely curable* by dextrose was questioned by both Marrack (1931) and Maitland (1932), on

the basis of much experience. It was not doubted by these latter authors, however, that dextrose given intravenously or rectally, or by mouth if it can be retained, is helpful in some instances.

Cathartics.—The normal individual should be warned that he is likely to [illegible]

[illegible]

subcutaneously, at the beginning of a sea voyage, during rough weather, or on the advent of a storm; this dose to be repeated twice, at hourly intervals, or until incipient dryness of the throat and disturbance of vision indicate its discontinuance. Lundy (1938) quoted the surgeon of the Italian liner *Rex* as saying that 1/60 grain (1.0 mg.) of atropine alone and given intravenously will almost instantaneously bring relief I believe that the attempts to prove the rationale of the atropine-strychnine combination, based upon the pharmacologic actions of its components, have not been fortunate; but it is certainly a clinical fact that the mixture does often relieve seasickness During War II a preparation much used in our Forces was known as the Army Motion Sickness Preventive, which contained 60 mg of sodium amytal, 0.4 mg. of atropine [illegible]

[illegible]

in experimental seasickness in man.

Scopolamine (Hyoscine).—Holling *et al.* (1944), studying the matter under conditions of good control in the British Navy during War II, found scopola- [illegible]

[illegible]

ing side effects other than some drying of the mouth on the higher dosage Hill and Guest (1945), of the British Army, also came out of a large-scale study with a preference for scopolamine

The only report of the use of scopolamine in the prevention of airsickness that has come to my attention is that of Haslam (1941), who wrote that he had been prescribing scopolamine with great satisfaction to his patients for a good many years. For short journeys he found that it sufficed to give 1/200 grain (0.3 mg) four hours before starting and another dose of the same size as the flight began; for long air journeys he advised three doses at four-hour intervals.

Benzedrine (Amphetamine) Sulfate.—Hill (1937), of the prewar *Aquitania*, used [illegible]

was [illegible]

ing [illegible]

in 16[illegible] patients with adequate controls. Relief of varying degree was noted in [illegible] per cent of the patients, the drug being used in the dosage of 10 mg. *before* arising and 5 mg (in a few very severe cases 10 mg) twice more during the day [illegible]

[illegible]

several times saw chloretone in 5-grain doses succeed when other sedatives had failed.

Psychotherapy.—Many individuals, especially first-trippers, agitate themselves into a very nervous state before they board ship and are almost certain to develop seasickness as soon as the ground swell is felt. In these cases it is perhaps advisable to use small doses of the sedatives for several days before the voyage is begun, advising the ship surgeon when possible what has been done in order that he may be guided in his medication during the first few days at sea; indeed, the carrying of a note to this officer, with a request for what is looked upon as "special care," often has a profoundly helpful effect upon nervous individuals who dread the ordeal of a bout of seasickness alone on a large ship; upon the reaction of the plagued surgeon let us draw the charitable curtain!

With regard to airsickness, Witwer (1944) stated that in a study of this malady in 1000 trainees during War II the impression was gained that fear and nervousness accounted for almost all of the cases, which indeed seemed to be borne out by the observation that 70 per cent of the airsick pilots obtained some relief from placebo medication. However, it is well known that dogs, horses, cattle and sheep become seasick, though to be sure we cannot say that the same causative factors do not operate here also.

Helpful admonitions regarding conduct during an ocean voyage are the following: (a) divert yourself in the company of others as much as possible, but do not plunge too strenuously into unwonted exercise; (b) look shipward instead of seaward for the first few days, but do not "strain" yourself to do this else it will only serve as a reminder of the ever-lurking illness; (c) avoid the sight of sick individuals as much as possible; (d) go in jauntily to meals as soon as they are announced for procrastination often spells disaster at this juncture; (e) if on a small ship, keep to windward of the deckhouse in order to avoid the odor of cooking food.

GERIATRICS

(The Care of the Aged)

In recent times there has come to be a certain amount of fuss and bother

haps I should be. My "objections," if one wishes to call them that, are two, which will be developed below

In the first place the analogy between pediatrics, the medical science at the one end, and geriatrics, the medical science at the other end of the span of life, is basically unsound. The reasons for this basic unsoundness have been expressed by Kniskern (1940) so much more ably than I could do it that I

will reveal that there are very few entities that can be placed categorically in this class. Barker's (1939) 240 aged patients presented with the following complaints in the vast majority of instances. disturbances of the nervous system, disturbances of the digestive system, disturbances of the circulatory system and disturbances of the locomotor apparatus. Barker furthermore said

organ systems and from accidental injuries. Of course one needs to particularize a bit among these categories but there is certainly nothing very distinctive in this list. Therefore in what follows I shall merely have a little to say with regard to these entities and such other matters bearing upon geriatrics as seem to come within the province of this book, warning the reader in passing that not even the merest trickle from the fountain of youth will splash him as he turns the pages.

Circulatory Disturbances.—There is a chapter upon this subject elsewhere in the book, in the course of which such considerations as bear upon the age of the patient are given what I hope is due consideration. There is really nothing else to add at this place.

Respiratory Disturbances.—This subject too has a chapter of its own, and such of the entities as are of an infectious nature are discussed separately under their own titles in the chapter on infectious diseases. One might remark that tuberculosis causes death among the very aged only occasionally and that

emphysema, which may lead to circulatory breakdown through overburdening of the right side of the heart, remains a serious problem.

Nephritis.—This subject, in both its acute and chronic phases, is discussed elsewhere in the book in a chapter of its own.

Gastro-Intestinal Disturbances.—These ailments too have their own chap- ... that it is the consensus that peptic ulcer

occurrence than among younger individuals. A note worth adding here is that the accelerated pulse indicative of continued bleeding may not occur in the aged. Meyer (1940) pointed out that if the activity of the ulcer is dependent on the digestive action of free hydrochloric acid and pepsin one would expect fewer perforations in the aged because of the diminution in the acid and enzyme; still, relatively more perforations occur. Dyspepsia in the aged, a less serious seeming matter, should nevertheless be investigated, for often dyspeptic symptoms are merely the signpost pointing toward the heart as the real cause of the trouble. Ivy (1939) said there is no reason to believe that constipation is more common in the aged than in younger individuals, remembering that constipation as a complaint may be present in a patient when true constipation is not. Nevertheless, rectal constipation often leading to fecal impaction is seen with greatest relative frequency in institutions for the aged, according to most observers. If soapsuds or milk and molasses enemas will not relieve the impaction, manual removal must be resorted to. Lee (1944) expressed himself as a firm believer in colonic irrigation about once a week for elderly people. ... radiologic diagnosis, but divertic- ... gives rise to ... considered a ... the majority of these lesions have become localized and resolved without extension or complications.

Finally, what to do with the aged individual whose symptoms point toward the need for a thorough gastro-intestinal study? Meyer (1941) well pointed out there is a deplorable tendency to employ merely simple symptomatic

cocky youngsters.

Cancer.—Despite the contrary opinion of some kind friends of my book it still seems to me that this great subject, being still in essence surgical, is not one that I should include. However, a few notes regarding intractable pain seem in order

New Methods of Employing Opiates.—The great drawback to the opiates is of course the fear of causing addiction, not that we are desirous of avoiding

this for its own sake since these patients are but waiting to die anyway, addiction brings with it symptoms of its own and often so alters the patie personality as to make the final ordeal additionally difficult for the fami furthermore, addiction implies diminishing analgesic returns per grain morphine, dilaudid, or pantopon, and the cost of the necessarily large amoun of these drugs is often very great. Recently two measures have been describe that merit mention here even though a thorough trial of them has not been made as yet One is the combination by Slaughter *et al* (1940) of morphine and prostigmine methylsulfate, they gave a reduced dose of morphine in 1 cc. of 1:2000 solution of the prostigmine salt and reported an apparent potentiation of the action of the morphine The other is the employment of small morphine dosage by continuous intravenous drip, as described by Neuhof (1941). Morphine sulfate, in the quantity of $\frac{5}{8}$ grain (40 mg), is added to 1000 cc. of physiologic saline solution and 100 cc of this solution (containing 1/16 grain, 4 mg, of morphine) is given intravenously per hour continuously. This method was described for postoperative use, but I think that it might be made to fit into some desperate terminal cancer pictures since Neuhof ascribed to it remarkable analgesic action with almost complete absence of the other and objectionable morphine effects, of course for one already addicted the dosage would doubtless have to be raised considerably

Cobra Venom.—This agent is very rarely of value but under some circumstances it may be worth trying on the off chance that it will give relief Unlike the opiates it must be given over a considerable period before relief may be expected; thereafter the doses are given less often in order to maintain the effect. Greenhill's (1941) routine is typical begin with 2½ mouse units injected intramuscularly, raise the next day to 5 or 10 units, and continue this dosage daily for about a week; thereafter, if analgesia has been obtained the patient may be kept comfortable with two or three injections weekly, but if success has not been obtained by the initial seven days of injection it is useless to persevere. Cobra venom is said sometimes to cause nausea, vomiting and iarrhea and occasionally intense pain at the site of injection

Intraspinal Alcohol Injection—It now seems to be established that in the jority of instances intraspinal alcohol injections give relief that may last eral months Of course this is a radical procedure since the spinal cord be injured, but the risk may certainly be taken in such cases as are under ent consideration In the chart on a succeeding page, published by the ess of Dr E. L Stern, of New York City, the sites for injection are . In what follows I present Greenhill's technic for injection in cases ic malignancy to serve as model for this procedure

preliminary medication is given because we wish to observe the im effects of the injection Most patients with advanced carcinoma of the gans have much more pain on one side than on the other The patient on the side opposite to that where most of the pain is present. A pad is placed under the pelvis and side to elevate the sacral and rtions of the spine, the back is arched as much as possible, the body omewhat ventrally, and the head is lowered slightly By placing the his attitude we raise the sacrolumbar region of the spine to the l and at the same time make the posterior or sensory nerve roots ly The anterior or motor nerve roots come to lie in a plane which of reach of the alcohol Even if the motor nerves are not removed of the alcohol, as occurs in the cauda equina, they are not often

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Organ involved		Type of block.	Site of injection.
Head		Trigeminal block	I, II, III divisions: (a) Terminal nerves (b) Subganglionic block (c) Gasserian ganglion block
		Stellate ganglion sympathetic block	(a) Paravertebral, between first and second ribs (b) Subarachnoid T 1-2 Especially important in connection with trigeminal pain or neuralgia
Neck		Cervical plexus block	Paravertebral
Upper extremity		Subarachnoid block	T 2-3 Exceptional, T 1-2
Chest	Larynx Trachea Bronchi Lungs Heart†	Subarachnoid block	T 3-4
	Aorta† Esophagus†		Upper part T 3-4 Lower part T 8-9
	Pleura		Entire T 6-7 or T 7-8 Upper part T 3-4 Lower part T 8-9
Abdomen	Aorta† Spleen	Subarachnoid block	T 5-6
	Stomach† *Liver*† Pancreas† Small intestine†		*T 6-7 or T 7-8*
	Colon†		T 11-12 or T 12-L 1 Ascending and transverse colon T 4-5
	Kidney-suprarenal gland		T 11-12
Pelvis	Ovaries Testicles Uterus† Tubes Ureters Seminal vesicles Prostate† Urethra† Bladder†	Subarachnoid block	T 12-L 1 and L 4-5
	Rectum—anus†		L 4-5
Lower extremity		Subarachnoid block	T 11-12 (Sympathetic) and L 1-2 (somatic)

* In blocking the long viscera, aorta, small and large intestines, or *in special cases, it may be necessary to repeat the block one or several segments* higher or lower than the levels given above.

This outline applies only to the adult body.

† Lesions affecting these organs usually involve the sympathetic nerves of both sides. Bilateral (right and left) injections should be given in these cases.

affected because sensory nerves are more susceptible than motor fibers to the effects of alcohol.

"Someone should hold the patient in the proper position. A weak solution of iodine or other antiseptic is applied over the lumbar and upper sacral regions. Injection is made in the second, third or (usually) fourth lumbar interspace. An ordinary lumbar puncture needle with a stylet is used. The needle is inserted into the desired interspace just as for an ordinary lumbar puncture, and novocain is injected into the skin before inserting the needle. After the needle is in the subarachnoid space, as evidenced by the flow of spinal fluid, 0.75 cc. of absolute or 95 per cent alcohol is injected into the cerebrospinal fluid. For this purpose it is best to use a tuberculin syringe in order to make sure that not more than 0.75 cc. of the solution is injected. Furthermore, the alcohol must be injected very slowly, drop by drop, allowing about two minutes for the injection of the 0.75 cc. The alcohol rises immediately to surround the posterior roots because the specific gravity of alcohol is about 0.806, whereas that of the spinal fluid is 1.007 to 1.011. No attempt should be made to draw spinal fluid into the syringe to mix it with the alcohol; in fact, this is exactly what is not wanted. After the injection is made the needle is withdrawn and the puncture hole is covered with sterile gauze and adhesive.

"Before the injection is completed, the patient will complain that the upper leg feels numb or hot, and that the leg cannot be moved. The *numbness* is almost routinely experienced after the injection but disappears spontaneously after a few hours or few days in most instances. In spite of what the patient says concerning inability to move the leg, when he is requested to move it he will meet no difficulty. At the time the patient informs us of the numbness he also often tells us, either voluntarily or in answer to our query, that the pain has disappeared. The longer the patient is permitted to lie on the side, the better the results. Hence, the patient should be kept on the side for two hours fter the injection, after which period he is permitted to get up and walk round. Sometimes a patient finds difficulty in getting up from a chair because s 'leg is asleep.' In other instances the leg feels heavy and the patient expences some trouble in walking up steps because the knee flexes readily. These sations usually wear off in a few hours, although in some patients they last umber of weeks.

"Nearly all of the patients who are ambulatory may be permitted to go e within three hours after the injection. No ill effects will be observed from procedure. It is perhaps best, however, to keep a patient in a hospital for ty-four hours after an injection. I should like to emphasize that the intral injection of alcohol may easily be carried out in a patient's home. This portant to remember because many individuals with cancer are bed at home and there is no need to subject them to the inconveniences and e of transportation to a physician's office or a hospital.

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Fractures.—The breaking of a bone, which used to be viewed as an unmitigated calamity for an oldster, is nowadays not nearly so serious a matter, thanks to the orthopedic surgeons who are insisting upon active movements immediately after recovery from the anesthetic.

Prostatism.—Here
trophied prostate, a
Spinal anesthesia, the

well!

Other Surgical Matters.—In this field, which is likewise outside the province of this book, great advances have also been made so that nowadays even elective surgery is performed in individuals of quite advanced years. Some factors that have contributed to this happy state of affairs in recent times are: (a) recognition of the necessity for painstaking preoperative measures to prevent postoperative complications by eliminating them "at the source" where possible; (b) the gradual passage of anesthesia into trained hands coupled with the introduction of less toxic general anesthetics and the increasing employment of spinal anesthesia; (c) postoperative care designed to oppose atelectasis by ensuring complete ventilation of the lungs, *i.e.*, the inhalation of carbon dioxide at intervals; (d) the attempt to prevent pulmonary embolism through centripetal massage of the legs and active and passive movements of the limbs in order to promote venous return as much as possible; (e) recognition of the necessity to get these old people up out of bed and moving around on their own power as soon as possible in order not only to prevent thrombosis but also the type of cardiac failure that may result from loss of cardiac reserve while lying in bed (and old people become terribly depressed in bed, too, feeling that now at last their time has come); (f) the recognition that fluids should be "pushed" only very slowly if at all in these patients and

Eyes and Ears.—Cataract and glaucoma, and degenerative and vascular changes of the eyes, are predominantly diseases of the aging and the aged. But it cannot be expected that a discussion this nature.

wn for some time that hydrochloric acid and pepsin secretion decrease with advancing years, and now recently the information has been added that salivary and pancreatic (except amylase) secretions also diminish. But Meyer and Necheles (1940), who carefully studied these matters, found that the secretory mechanisms are capable of response under adequate stimulation and that the quantitative alterations apparently do not affect intestinal digestion. They concluded that restrictions imposed on old people because of fear of inadequate digestion of carbohydrate, protein, or fat do not appear warranted. In other words, old age in itself is no reason for dietary alterations. Experience has shown in fact that with few exceptions old people select both the quantity and quality of food that satisfies their needs and taste, and I do not think there is much fact to support Tuohy's (1943) warning that they should eat very sparingly of fats. Loss of appetite, however, is a matter often requiring serious attention. It may

be due to loss of teeth or poorly fitting false teeth that necessitate a change to a soft unattractive diet and ultimately lead to a loss of interest in food. Then, too, there are changes in the taste buds and diminution in the senses of sight and smell. To stimulate such lagging appetites bitters have long been used before meals, such as a teaspoonful in water of the compound tincture of either cinchona or cardamom, or a little dry wine to be taken with the principal meal of the day. Lee (1944) said he had come around again to a belief in the efficacy of "digestive assistants" in the elderly, *i e*, hydrochloric acid, pepsin, pancreatic extracts and the bile salts. I imagine not many observers would agree with that position Latterly, thiamine hydrochloride (vitamin B,) has begun to be used with apparently excellent results—dosage is usually a 3-mg tablet after meals once, twice, or thrice daily as indicated by results There are undoubtedly cases in which the prohibition of tobacco smoking would be helpful in stimulating the appetite, but the advisability of attempting such a radical deprivation must be carefully weighed in each individual case In this group of elderly individuals with jaded appetites, and especially in those with dietary restrictions self or otherwise imposed, true vitamin deficiences can now and then be found

Disturbances of Locomotion.—In speaking of the infirmity of old age we probably most frequently have in mind the weakness in the legs and difficulty in locomotion that so often accompany the state It seems that stiffening of the joints results to a considerable extent from failure in lubrication as well as from aging of the nerves and muscles Some of the cases are of course due to osteo-arthritis, fibrositis, or gouty arthritis—subjects that have a section of their own in the book And then there is the group of cases lying entirely within the realm of the neurologists, the relatively rare cases of senile paraplegia and senile cerebellar and amyostatic syndromes, I believe there is nothing to do for these latter save make the diagnosis

Neuropsychiatric Disturbances.—Many old people develop tremor, particularly of the head, that is very annoying and embarrassing to them, but about the best one can do in these cases is to give assurance that the shaking is not a forerunner of paralysis agitans and is not as noticeable anyway as the patient hinks it is True paralysis agitans with its characteristic flexed position of the xtremities, bent-over posture, shuffling gait and general rigidity combined with tremor is a truly unfortunate affliction for which practically nothing can be done. It seems to me that all of the operations that have been tried so far are still entirely in the experimental stage The drugs used to combat postencephalitic parkinsonism are of course tried (see Encephalitis), but their effectiveness is usually slight here If every effort is made to remain active both physically and mentally it is sometimes surprising to observe the small extent to which his degenerative process limits the individual's participation in daily affairs he tendency to become dependent upon another, usually the husband or the fe, for the performance of most acts must be rigorously opposed from the ginning

The aged often do not sleep well at night, being not so much disturbed in their sleep as simply sleepless Sometimes daytime napping makes up some of the loss, indeed this is almost universally the case However, insomnia in the aged, though often the subject of bitter complaint, is rarely a matter of serious concern for it seems that the aged body actually requires to spend a smaller proportion of the twenty-four hours in slumber than does that of the person in early or middle life The happiest solution is for the aged individual to find

something to do—read, play solitaire, etc.—*while the younger members of* the family are getting their needed sleep. Certainly one should be very chary of employing hypnotics in these oldsters for they sometimes react in a very excited manner to these drugs; the bromides and barbiturates seem to be the worst offenders in this respect. Alcohol is the safest nightcap if one is to be *employed at all.*

The mental de [illegible] to require more [illegible] either ideas, fooc [illegible] excessive worry about the financial future; suspicious tendencies; and an increasing sensitiveness, so that we say "grandma is so easily 'hurt' nowadays." The summed expression of these things depends entirely upon the individual and the family environment—if luck is good the oldster may become the dearest and most charmingly influential member of the household; but luck is not always good.

The true senile psychoses must be left to the psychiatrists, it seems to me. They have done a deal of describing and classifying of them, and certainly should be called in before the awful step is taken of committing any patient. Some alleged senile psychoses have turned out to be only toxic states that have cleared up under proper eliminative and supportive therapy. I believe it is now the consensus that Robinson (1941) was correct in stating that shock therapy may be safely employed in the aging individual and that in some instances the senile process seems to be arrested.

DISEASES OF THE SKIN

IMPETIGO CONTAGIOSA

Impetigo is an acute contagious disease of the skin with a predilection for the face. It is sometimes spread among adult males by barber-shop infection, and an occasional case is seen in an adult female, but the great majority of patients are children within the school years There are a number of varieties of this malady, but the most common one is characterized by a sudden crop of localized erythematous areas, upon which rapidly appear thin-walled vesicles and bullae; these lesions soon become pustular and then dry up quite rapidly, leaving thin, honey-colored, loosely attached crusts that drop o without scar formation, though the hyperemia fades out of the affecte areas rather slowly There is usually no itching Both staphylococci and streptococci have been obtained from the lesions Impetigo is usually much worse in hot humid climates

THERAPY

Penicillin.—The use of this agent has completely revolutioniz... ment of impetigo For example, in a compa... agents, Robinson and Robin... illin ointment effected ... racin ointment in seven days, am... ent in 8 days, and tyrothricin ointment in 12 days Th... the technics of employment ... wing summaries of typical reports will present

Finkle (1947) reported the cure of ten patients in an average time of 4.9 days with the use of penicillin intramuscularly in the Romansky formula; eight patients were cured with two injections on succeeding days and two patients required three injections. In connection with the intramuscular employment of penicillin, Pillsbury (1946) advocated thorough gentle cleaning of the involved site by means of soap and water, compresses of isotonic solution of sodium chloride or 0 1 per cent potassium permanganate solution for twenty minutes two to six times a day, gentle mechanical opening of all pustules, and careful removal of soft and cutaneous debris. Brett (1946) reported complete cure in eighteen of nineteen cases with such widespread lesions that it was considered advisable to admit them to the ward; these were soldier cases seen in the Southwest Pacific Penicillin was given intramuscularly, all new vesicles were ruptured with cotton applicators dipped in 10 per cent silver nitrate solution, and all crusts were removed daily; penicillin ointment was applied locally three times a day. The water-soluble ointment found most satisfactory in the hot climate was the following:

℞ Tragacanth.	20
Glycerin	200
Water	200

The tragacanth was mixed with 30 cc of glycerin and added to the remainder of the glycerin. To this 100 cc of water were added and mixed To the remainder of the water 100,000 units of penicillin were added and the whole thoroughly mixed

Hopkins and Lawrence (1946) reported that in fifty-two cases of impetigo involving the head and neck, and thirty-five cases of the bullous or tropical type involving chiefly the covered portions of the body, especially the axillae, results from the use of penicillin were almost uniformly good whether the treatment was topical or intramuscular. They said that many cases were much improved overnight, that nine appeared well in three days and that the medium time for clearing was six to seven days. Indeed, in the sixteen cases failing to respond they felt there were apparent explanations for the failures in all instances. Out of a considerable study of penicillin concentration in ointments, Waisman and Gots (1946) concluded that there was no advantage in a concentration of penicillin higher than 300 units per gram of ointment. They also said they were not convinced that one ointment base was superior to another with equivalent concentration of penicillin and that they felt they were getting just as satisfactory results with a base of simple petrolatum as with any other.

Aldrich and Holmes (1946) reported the satisfactory treatment of ten cases of impetigo neonatorum with intramuscular administration of penicillin, the babies being returned to the nursery with the other children within thirty-six hours of the beginning of treatment; the routine therapy recommended as a result of this experience was immediate isolation and two doses of 5000 units of penicillin each with a three-hour interval, the traditional use of local treatment of some sort being a matter of choice. Kendig and Fiske (1945) reported that in fourteen cases of impetigo neonatorum treated with penicillin ointment containing 333 units to the gram, all the lesions appeared to be dry and healed after a maximum of three days, though in three instances there was a recurrence after the patient had been home from the hospital more than a week.

Hopkins and Lawrence (1946) reported that some form of cutaneous reaction to penicillin appeared in all of the 618 soldiers with pyogenic dermatoses treated by them with penicillin during War II; they said, however, that during the brief treatment required for impetigo these sensitizations seldom interfered with the success of the treatment. However, Pillsbury (1946) felt that the total period of local application should not exceed five days even at the risk of relapse.

Other Agents.—With penicillin apparently securely in the ascendant, I merely give brief listing to some of the other preparations. *Sulfonamides.*—Fairly good results are obtained from the local application of these agents, particularly sulfathiazole, but it is nowadays recognized that the risk of sensitizing the patient is too great to justify this therapy. Furthermore, Smith and Jones (1945) found an occlusive dressing with calamine liniment equally as effective as the local application of sulfathiazole and free from the latter's danger. *Furacin.*—Downing *et al.* (1947) reported that in twenty of twenty-six cases treated with furacin soluble dressing, applied four times daily without covering except when necessary to protect the clothing, the lesions were healed within one week. They found that if a light covering was secured over the face the dark-brown discoloration of the dressing caused by exposure to light was prevented and the solution was kept in the proper place. Robinson and Robinson
furacin ointment in the same
(1946) reported that the applic

and tyrothricin ointment, effected response in an average of six days in eight cases; but twelve days was required for cure with this agent in ointment in

painted on the lesions in 1 to 2 per cent aqueous solution. *Quinoline Compounds.*—*The Military Manual of Dermatology (1942) recommended the* application two or three times daily of the following ointment:

	Gm or cc.
Chlorhydroxyquinolines (mixture)	0 5
Benzoyl peroxide (explosive)	10 0
Oil of white thyme	0 65
Eucalyptol	1 3
Petrolatum,	
Anhydrous lanolin, of each, to make	100 0

D'Alibour's Solution.—This consists in 1½ grains (0 1 gm) of copper sulfate and 3 grains (0.2 gm.) of zinc sulfate to the ounce (30 cc) of camphor water; it is sopped on to the lesions several times daily after the crusts have been removed.

TINEA VERSICOLOR

This malady is characterized by the presence, usually only on the chest and shoulders, of a yellow or brown macular eruption that sheds very fine scales. There are usually one or more large plaques with numerous small lesions round about them. Itching is slight or entirely absent. The disease, which is caused by *Microsporon furfur*, is rather common among men, but is entirely harmless. A few cases involving the scalp have been reported in Europe and in both North and South America, a distribution that is said to be fairly common in the Far East.

THERAPY

appearance of mold. Crocker, cited by Sutton, found the use of 5 per cent solution of thiosulfate, followed by 3 per cent solution of tartaric acid, to be even more efficacious.

ERYTHEMA MULTIFORME

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the face, neck, arms, hands, legs and feet. Except for the extremely rare instances in which there are serious systemic manifestations, subjective symptoms are few or none, but the attack sometimes lasts several weeks; the aver-

age time spent in hospital by Duemling and Lesney's (1945) patients was eleven days, the longest duration of symptoms twenty-one days and the shortest six days. Susceptible individuals may be affected with this disease time and

men feel that the attacks are often due to a toxemia of intestinal origin. Anderson (1945) stated his feeling that there might be an etiologic relationship between erythema multiforme and herpes simplex, but the dermatologists discussing his paper did not seem inclined to support the hypothesis on the basis of either clinical or experimental observation.

THERAPY

Inquiry into what drugs are being taken should be made; arsenic, mercury, the iodides and phenolphthalein seem to be the chief offenders Dieting and the taking of copious amounts of water are sometimes of value; perhaps the newer approach to food allergy might well be tried in recurring cases. At the New York Skin and Cancer Hospital we used always to give an initial dose of castor oil and then keep the patient on the Bulkley diet of rice (without sugar or cream), bread, butter and water as long as he would cooperate— ... fluids was thought to lessen considerably

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believe that any

of the dermatologists are considering it to be a specific in these cases.

EPIDERMOPHYTOSIS OR DERMATOPHYTOSIS

(Ringworm of the Hands, Feet, Groin, Axillae, Breasts and the Hairless Skin Generally)

This is a skin disease that in one form or another seems to afflict most people all over the world, being especially prevalent in moist tropical regions; indeed, during War II in some instances it posed a rather serious military problem. *Trichophyton gypseum* and *T. purpureum* are most frequently recovered from ... less often. Dermat-

mat-

foot"

on the fingers,

(eczema margin.

definitely marginated lesion occurring principally in the groin ... axillae and beneath the breasts; and the other (tinea circinata, ringworm of the body), the slightly elevated ringlike patches that occur principally on the face, neck and hands; and (3) macerated, the familiar lesion between the fingers or toes and beneath the breasts, presenting as an area of clean, white, sodden tissue of a varying degree of thickness There are several other forms less frequently encountered.

The disease is certainly contagious but the problem of protecting against it, seeing its ubiquity and protean character, is a very difficult one indeed

THERAPY

Treatment of epidermophytosis has never been entirely satisfactory, some cases resisting any and all sorts of measures, while others clear up very quickly under the simplest treatment (I distinctly remember cases, seen while working in Williams' clinic at the New York Skin and Cancer Hospital, that rapidly [illegible]

[illegible]

condensing here the recommendations of Pillsbury *et al* (1942), in the Manual of Dermatology published for the Armed Forces under the auspices of the National Research Council, merely appending short notes on penicillin, ethyl chloride, and the fatty acids.

Active Acute Stage.—Whenever possible hot potassium permanganate soaks should be used for twenty minutes three times daily, employing the solution made by dissolving one 5 grain (0.3 gm.) tablet of potassium permanganate in 3 quarts of water. Much stronger solutions (up to 6 per cent) may be painted on areas of ringworm on the body After the potassium permanganate soaks, the following lotion (shake) should be applied·

Sulfur	ʒi	4 0
Resorcin	ʒss	2 0
Zinc oxide	ʒvi	25 0
Talc	ʒvi	25 0
Bentonite	ʒi gr xv	5 0
Water (or water and alcohol equal parts)	ʒii	60 0

Twice daily the fissures should be painted with 5 per cent silver nitrate solution. If there are vesicles they will have to be aseptically opened before [illegible]

th [illegible]

[illegible]

Pragmatar Ointment

Sulfur	gr xlv	3 0
Salicylic acid	gr xlv	3 0
Cetyl tar distillate	ʒi	4 0
Duponol	gr xv	1 0
Petrolatum	ʒixss	38 0
Stearyl alcohol	ʒivss	18 0
Cetyl alcohol	ʒi gr. xlv	7 0
Mineral oil	ʒvi gr xv	25 0

Whitfield's Ointment (One-Half Strength)

Salicylic acid	3 per cent
Benzoic acid	6 per cent
White ointment (U S P. XIII) to make	

In some cases in the subacute stage one may cautiously apply one of the following, the first being known as Castellani's Paint:

Saturated alcoholic sol basic fuchsin	10 0
Aqueous solution phenol (5 per cent)	100 0
Filter and add:	
Boric acid	1.0
After two hours, add	
Acetone	5 0
Two hours later, add	
Resorcin	10 0
This preparation does not keep over one month	

Salicylic acid	3 0
Thymol	1.0
Alcohol (70 per cent) to make	100 0

Chronic Stage.—The lesions on the body do not tend to become chronic. Those between the toes and on the feet do very frequently resist treatment and assume one of the following forms: if in between the toes the lesions are [illegible] patches with fissuring; or there may be thickened [illegible] les; [illegible] and along the sides of the feet. For such chronic cases the list of recommended agents is increased by the following:

Deek's Ointment

Salicylic acid	2.0
Oil of eucalyptus	12 0
Bismuth subnitrate	12 0
Wool fat,	
Ammoniated mercury ointment, of each, to make	100 0

Apply at bedtime only.

Dioxyanthranol Ointment

Anthralin (or cignolin)	0 1–1 0 per cent
Petrolatum to make.	

Apply cautiously once or twice daily to chronic hyperkeratotic and scaling plaques

Chrysarobin Ointment

Chrysarobin	0.1–0.5 or even 5 0 per cent
Petrolatum to make.	

The chrysarobin must be fresh and the ointment freshly prepared.

These chronic lesions should be kept clean, and if necessary hyperkeratotic material is to be removed by the use of sandpaper, curets, scissors, or the like. Superficial x-ray therapy has been said to be helpful in selected cases.

Ethyl Chloride.—In 1929 Taylor reported excellent results in a small series of cases in which he froze the lesions with the ethyl chloride spray; Bograd (1943) stated that in the South Pacific during War II the ethyl chloride treatment of lesions of the tinea group gave uniformly excellent results; and Taylor (1946) again stated his belief that refrigeration with [illegible] to any other physical [illegible] said that at the New [illegible] ide led to conclusions about like those of Lewis and Morginson [illegible] found that the agent effects immediate clinical improvement, with subsidence of vesicles and pustules, healing of denuded areas, increased dryness of the skin and re-

In some cases in the subacute stage one *may cautiously apply* one of the following, the first being known as Castellani's Paint:

Saturated alcoholic sol. basic fuchsin	10.0
Aqueous solution phenol (5 per cent)	100.0
Filter and add.	
Boric acid	1.0
After two hours, add	
Acetone	5.0
Two hours later, add	
Resorcin	10 0
This preparation does not keep over one month.	

Salicylic acid	3 0
Thymol	1.0
Alcohol (70 per cent) to make	100 0

Chronic Stage.—The lesions on the body do not tend to become chronic. Those between the toes and on the feet do very frequently resist treatment and assume one of the following forms: if in between the toes the lesions are likely to be sodden, odorous patches with fissuring; or there may be thickened hyperkeratotic plaques with scaling, fissuring, or even vesicles on the soles; or red, thickened and indurated dry plaques on the sole, around the heel and along the sides of the feet. For such chronic cases the list of recommended agents is increased by the following:

Deek's Ointment

Salicylic acid	2 0
Oil of eucalyptus	12.0
Bismuth subnitrate	12 0
Wool fat,	
Ammoniated mercury ointment, of each, to make	100 0

Apply at bedtime only.

Dioxyanthranol Ointment

Anthralin (or cignolin)	0 1–1 0 per cent
Petrolatum to make.	

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Petrolatum to make	

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Ethyl Chloride.—In 1929 Taylor reported excellent results in a small series of cases in which he froze the lesions with the ethyl chloride spray; Bograd (1943) stated that in the South Pacific during War II the ethyl chloride treatment of lesions of the tinea group gave uniformly excellent results; and Taylor (1946) again stated his belief that refrigeration with ethyl chloride, properly employed, is definitely superior to any other physical or chemical application. However, Montgomery (1945) said that at the New York Skin and Cancer Unit their trial of ethyl chloride led to conclusions about like those of Lewis and Morginson (1944), who found that the agent effects immediate clinical improvement, with subsidence of vesicles and pustules, healing of denuded areas, increased dryness of the skin and re-

gression of hyperhidrosis, but that since recurrences were experienced in most of their cases within ten days after cessation of treatment, it was felt that the best use of ethyl chloride was as an adjunct to the customary management of these cases since it seems to produce an antagonistic environment for the fungi through promoting dryness of the skin. Upon the other hand, Bograd stipulated that no other drugs be used in conjunction with ethyl

margins hiding the vesicles, the whole raised margin is sprayed once daily for two successive days, and with the disappearance of the inflammation the discrete vesicles that become prominent are treated as though they were primary lesions With the more resistant lesions of the hands and feet, the first few sprayings are also applied only around the margin of the lesion, and as healing proceeds, islands of denuded epithelium are then separately sprayed

Penicillin.—Hopkins and Lawrence (1946) felt as a result of extensive trial of penicillin that it is in some instances effective in clearing up secondary infection and thus probably to some extent increasing the frequency and rapidity of cure. Pillsbury (1946) said that in his opinion penicillin should be injected and not be applied locally.

Fatty Acids.—During War II, the fungistatic activity of fatty acids was studied by numerous investigators, and it was found that apparently the most effective preparations were propionic, undecylenic and caprylic acids and the soaps of the same. A great deal of enthusiasm was worked up for the employment of these preparations, but it does not seem to me from the reports that their very great superiority to any of the other agents has as yet been definitely shown For example, Hopkins *et al.* (1946), while able to report a high percentage of clinical cures in patients treated over four weeks with preparations of undecylenic acid, found that while the percentage of cures was distinctly higher than with most other fungicides, it was not superior to that achieved with sulfur and salicylic acid. They did find, however, that the percentage of patients irritated by undecylenic acid was lower than in the groups treated with the other preparations Following the time-hallowed dermatologic pattern, the literature with regard to the new fatty acid preparations is extremely vague and confusing. So far as I can make out from the paper of Hopkins *et al.* (1946), they obtained best results with an ointment having the following formula:

Undecylenic acid	5 0
Triethanolamine	3 0
Zinc peroxide.	10 0
Carbowax base to make	100 0

Keeney *et al.* (1945), as a result of comparative studies, recommended the use of a 10 per cent sodium caprylate ointment (the formula, prepared for them by Mycoloid Laboratories, Little Falls, New Jersey, is too complex to set down here)

PROPHYLAXIS

Where men are living under crowded conditions it was recommended by Pillsbury *et al.* (1942) that the Army-issue foot powder be applied to the feet and inside the footwear after a bath, or night and morning:

	Per cent
Salicylic acid	2 0
Boric acid	6 0
Zinc stearate	3 0
Exsiccated alum	1.0
Starch	10.0
Powdered talc.	78 0

Alternate formula

	Per cent
Zinc peroxide	10 0
Tannic acid	5.0
Boric acid	20.0
Bentonite	10.0
Talc.	55.0

During War II, Sulzberger and Kanof (1947) made a comparative study of a considerable number of formulae in the prophylaxis of epidermophytosis. The following two formulae are those of the powder and ointment respectively with which they seem to have obtained best results:

Undecylenic acid-undecylenate powder (pigmented)

	Per cent
Zinc undecylenate	20 0
Purified talc, U S P.	76 0
Undecylenic acid, grade AA	2 0
Dibenzo thio indigo (red)	2 0

Undecylenic acid-undecylenate ointment (pigmented)

	Per cent
Undecylenic acid, grade AA	5 0
Triethanolamine	3 0
Zinc undecylenate	18 0
Propylene glycol, N F	10 0
Carbowax 1500	19 0
Carbowax 4000	29 6
Distilled water.	15 0
Dibenzo thio indigo (red)	0 4

For large-scale prophylaxis [illegible] it is usual to employ in a compuls[illegible] diluted 20 to 1 and changed [illegible] seem that as a result of experience in War II, [illegible] skeptical of the value of sodium hypochlorite solution for the prophylaxis of epidermophytosis. Gould (1942) said that anywhere from a 3 to 10 per cent solution of sodium thiosulfate (the ordinary "hypo" of photographers) is just as satisfactory as the hypochlorite solution, but Warren (1943) in-[illegible] value sodium thiosulfate may have is likely due [illegible]

of shower rooms and barrack floors and the expos[illegible]

boards to sunlight where practicable than through the forced employment of any sort of prophylactic foot-bath solution

The findings of Nickerson *et al.* (1945) indicated that the wearing of sandals is an excellent measure for eliminating infection; they felt that probably the effect was due to aeration and to the prevention of accumulation of sweat

then to be wrapped up tightly in paper for twenty-four hours and are there-

the other There is no need of destroying clothing since materials of all sorts may be sterilized safely by first washing in the usual manner, then soaking in a 1:1000 solution of bichloride of mercury for a day, and afterward thoroughly rinsing in water before drying.

POMPHOLYX

(*Dysidrosis*)

This is a well-known affliction of many individuals during the hot summer months; its exact relationship to sweating is not understood, but significantly the lesions occur principally on areas where perspiration takes place freely—
oles. Pearly
g, and occa-
scratching.
stage takes
place but moderate desquamation and a yellowish-brown discoloration persist for several weeks In the soles and palms the vesicles usually lie very deep and make their presence known principally through the "shotty" feel they give to these regions.

THERAPY

Pompholyx may appear in an individual having epidermophyton infection or seborrheic or other eczema, in which cases the treatment is merely that of the primary disturbance. In cases unassociated with other lesions and merely occurring when the individual sweats excessively, one should be very chary of applying the "strong" type of preparations used in epidermophytosis as they will often only aggravate these idiopathic cases. Indeed, it seems that the treatment most productive of results here is to do nothing and pray for cool weather

RINGWORM OF THE SCALP

Ringworm attacks the scalp only in children. The patches are round and scaly, but not centrally involuted as in similar affections of the glabrous skin;

may be involved and the itching becomes quite intense; a few instances of involvement of the eyebrows have been recorded. Infections caused by *Microsporon lanosum* are much less resistant to treatment than those caused by *M. audouini*. The well-known spontaneous cure of *M. audouini* infections that usually takes place during puberty, and the immunity of the hair of adults to infection with this fungus, is explained by Rothman *et al.* (1947) on the basis of the fact that with the onset of puberty the sebaceous glands of the scalp start to secrete a sebum containing higher concentrations than before of low-boiling saturated fatty acids with selective fungistatic and fungicidal action on *M. audouini*. They feel that the "adult type" of hair fat does not kill the fungus spores in the hair but prevents infection in the new hair that follows the old infected hair in the process of shedding

THERAPY

Manual Epilation and Application of Fungicidal Agents.—This, the old treatment of ringworm of the scalp, is fairly effective in *M. lanosum* cases but *M. audouini* is much more resistant The hair must be clipped short and [illegible]

the head [illegible]
pooed ag[illegible]
the day a[illegible]
at least.

As a result of studies with the fatty acids during War II, Carrick (1946) reported the employment of the following formula with satisfaction:

Undecylenic acid	5 0
Triethanolamine-technical	1 75
Zinc undecylenate	20 0
Sodium tetradecyl sulfate	3 0
Anhydrous carbowax to make	100 0

In connection with these new fatty acid agents it is of interest to note that Miller *et al* (1946), discussing their trials of many therapeutic approaches during the epidemic of *M. audouini* infections that has been apparent along the Eastern seaboard in recent years, said that iodine and mercury seemed in their hands at the Vanderbilt Clinic in New York to be just as effective as the newer agents. Mercury is usually employed as a 10 per cent ammoniated mercury ointment. Iodine may be applied in one of the following forms:

Tincture of iodine	℥ss	15.0
Alcohol to make	℥ii	60 0
(Some men use the tincture undiluted)		
Iodine crystals	gr x	0 6
Thymol crystals	gr. x	0 6
Oil of cinnamon	♏x	0 6
Petrolatum to make	℥ii	60 0

Other older remedies are the following:

Chrysarobin	ʒi	4 0
Petrolatum to make	℥ii	60 0
(Careful of eyes!)		
Salicylic acid	ʒi	4 0
Precipitated sulfur	ʒi	4.0
Petrolatum to make	℥ii	60 0

Strickler (1946) reported good results from the employment of a mixture con-

and 0.8 per cent inorganic material, and Strickler said that this mixture is incorporated in cottonseed oil in the amount "2 gm of the iodine to 30 gm. of the cottonseed oil," though it is not quite clear to me just what he means by that statement At any rate Strickler reported cure of seventy-four of 115

patient was told to place a white paper in the hat when worn and to change the paper each day and burn it.

X-Ray Epilation.—There is no longer any doubt that preliminary epilation of the entire scalp by the use of x-ray, to be followed by the application of the antiseptics as above, is the best available treatment, especially in *M audouini* cases After the epilating treatment the hair begins to loosen in three weeks or more, and I believe it is the practice of roentgenologists to apply adhesive tape at this time and thus remove the hair. Steves and Lynch (1947) reported that of their 188 *M audouini* cases treated by x-ray epilation, 80 per cent were cured within three months, whereas of 298 patients treated by clipping and manual removal of the fluorescent hairs, only 25 per cent were cured within three months. Lewis *et al.* (1946), reporting on the clinical and laboratory study of 312 patients in whom the predominant fungus was *M. audouini*, said that x-ray epilation was responsible for 90 per cent of the cures McKee *et al* (1946) said that practically all patients are cured in four to eight weeks after the

in the hands of just *any* upstart operator of an x-ray apparatus; this is a special technic, and, like all special technics, requires study and practice in order to obtain mastery. It is not easy to forget the unfortunate sequelae of unskilled roentgen ray or radium therapy.

RINGWORM OF THE BEARD

The treatment of ringworm of the bearded region differs in none of its essentials from the treatment of ringworm of the scalp

may be involved and the itching becomes quite intense; a few instances of involvement of the eyebrows have been recorded. Infections caused by *Microsporon lanosum* are much less resistant to treatment than those caused by *M. audouini.* The well-known spontaneous cure of *M. audouini* infections that usually takes place during puberty, and the immunity of the hair of adults to infection with this fungus, is explained by Rothman *et al.* (1947) on the basis of the fact that with the onset of puberty the sebaceous glands of the scalp start to secrete a sebum containing higher concentrations than before of low-boiling saturated fatty acids with selective fungistatic and fungicidal action on *M. audouini.* They feel that the "adult type" of hair fat does not kill the *fungus spores in the hair but prevents infection in the new hair that follows* the old infected hair in the process of shedding

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at least.

As a result of studies with the fatty acids during War II, Carrick (1946) reported the employment of the following formula with satisfaction:

Undecylenic acid	5 0
Triethanolamine-technical	1.75
Zinc undecylenate	20 0
Sodium tetradecyl sulfate	3.0
Anhydrous carbowax to make	100 0

In connection with these new fatty acid agents it is of interest to note that Miller *et al.* (1946), discussing their trials of many therapeutic approaches during the epidemic of *M. audouini* infections that has been apparent along the Eastern seaboard in recent years, said that iodine and mercury seemed in their hands at the Vanderbilt Clinic in New York to be just as effective as the newer agents. Mercury is usually employed as a 10 per cent ammoniated mercury ointment. Iodine may be applied in one of the following forms:

Tincture of iodine	℥ss	15 0
Alcohol to make	℥ii	60 0
(Some men use the tincture undiluted)		
Iodine crystals	gr. x	0 6
Thymol crystals	gr x	0 6
Oil of cinnamon	♏x	0 6
Petrolatum to make	℥ii	60 0

Other older remedies are the following:

Chrysarobin	ʒi	4 0
Petrolatum to make	℥ii	60 0
(Careful of eyes!)		
Salicylic acid	ʒi	4 0
Precipitated sulfur	ʒi	4 0
Petrolatum to make	℥ii	60.0

Sulfur.—This drug may be used in the form of a simple sulfur ointment, as the following:

Precipitated sulfur	ʒi	4.0
White wax	ʒi	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ii	60.0

or it may be somewhat reduced in amount and combined with salicylic acid, as in the following, in which the salicylic acid may be doubled in amount if considered desirable:

Precipitated sulfur	ʒss	2.0
Salicylic acid	gr. x	0.6
White wax	ʒi	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ii	60.0

Resorcinol.—This drug is used either as ointment or lotion in the strength of 1 to 6 per cent, the following formulae, much used in my day at the New York Skin and Cancer Hospital, contain 4 and 6 per cent, respectively:

Resorcin	gr. xx	1.2
Petrolatum to make	℥i	30.0
Resorcin	ʒiv	15.0
Glycerin	℥i	30.0
Alcohol	ʒvi	24.0
Water to make	℥viii	250.0

Dark hair is not appreciably affected by resorcin, but the fact should be borne in mind that this drug will stain light, red, or white hair, especially if the patient exposes the head to the sunlight after its application. Resorcin monoacetate is said to be less likely to do so, it may be substituted for resorcin in equal amounts A satisfactory prescription would be written by replacing the chloral hydrate in the Johnston formula (see preceding page) by ʒiiss (10.0 gm.) of resorcin monoacetate

SYCOSIS BARBAE

(Barber's Itch)

The infection may persist for many months or years, and the resultant alopecia and scarring are sometimes quite considerable.

THERAPY

Here, as in the ringworm infections, the area must be epilated either by

the fine distinctions they would have made in the treatment of the tineal and staphylococcic infections. X-ray is said to cure about 40 per cent of cases It seems to be the consensus that penicillin is of little value in this disease.

SEBORRHEIC DERMATITIS

This is probably the commonest of all skin diseases, though it is most often troublesome in hot humid climates. In the scalp it is known as dandruff, which [illegible]

[illegible] tion other than the points mentioned is the sternal region; here the lesions are rounded, irregular, or circinate, and are covered with greasy yellowish scales The differentiation between seborrheic dermatitis, ringworm of the glabrous skin and psoriasis is not always easy to make. There may be much itching

THERAPY

The remedies for this condition are of course legion, which is simply an indication of the relative ineffectiveness of them all. However, any one of the following plans of treatment will lessen the severity of most cases; some will be "cured," though return of the lesions is almost certain. Many dermatolo- [illegible]

[illegible] esting studies of the effect of liver extract therapy in a group of cases showing seborrheic-like lesions but not the frank syndromes associated with deficiency in the various fractions of the vitamin B complex; he did not claim curative effect of liver extract in ordinary seborrheic dermatitis. The findings of Wright *et al.* (1943) indicated that if vitamin B complex therapy is to be of definite [illegible]

[illegible] week, being washed out with soap and water the next morning. The reader should be warned that a few instances of severe idiosyncratic reactions to ammoniated mercury have been recorded.

Ammoniated mercury	gr xlv	3.0
Salicylic acid	gr. x	0.6
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

This contains 5 per cent of ammoniated mercury and 1 per cent of the salicylic acid; the quantities may be doubled, giving 10 and 2 per cent respectively, but higher than this it is perhaps not advisable to go in the average case. On the nights when this ointment is not being used, Sutton advised the employment of the following lotion, which he accredited to Johnston:

Mercuric chloride	gr. ¼	0.01
Chloral hydrate	ʒij	8.0
Spirit of formic acid (N.F. VIII)	ʒiv	15.0
Castor oil	♏viij	0.5
Oil of bergamot to give odor		
Alcohol (80 per cent) to make	℥vi	180.0

covering surprisingly large portions of the body. In the intervals between attacks the skin usually clears entirely. *Distribution:* the eruption is symmetrical, and, from a beginning usually on the elbows and knees, may spread all over the body; the scalp is often involved, but the face and the backs of the hands are frequently spared even when the involvement elsewhere is very extensive.

Psoriasis is generally considered to be rare in the Orient and in the tropics, but Pardo-Castello (1934) said that it is of frequent occurrence in whites residing in Cuba, whose climate is subtropical Most patients in the temperate zones are better in the summer and worse in the winter. The disease is extremely rare in full-blooded Negroes and American Indians. Nothing is known of its etiology or of what part, if any, heredity plays in its causation. Swartz (1945) observed marked sensitivity to intradermal injections of minute amounts of an autogenous vaccine made from a certain strain of *Streptococcus faecalis*, the response being marked by a local reaction at the point of injection and an

series of 231 patients, about five times as many were overweight as were under-

Ebers, written about 1550 B.C.

THERAPY

While there are many cases of psoriasis that remain completely intractable ("an antidote for dermatologists' ego"—Bechet, 1936), the duration of the average moderately severe attack can usually be much lessened by proper local treatment. X-ray therapy sometimes causes temporary improvement,

ultraviolet light is usually ineffective, though there have been a few reports indicating that ultraviolet light with adjuvant photosensitization is more effective. Epstein's (1947) method consisted in treating the patient one to three times weekly as follows (a) a liquid containing 10 per cent crude coal tar and 20 per cent acetone in benzine is painted on the lesions on the morning before and on the morning of the treatment, and in addition 5 grains (0 3 gm.) of sulfanilamide is administered orally four times on the day before the treatment; (b) the patient is then exposed to generalized radiation from a hot quartz lamp without filtration, the initial exposure consisting of suberythema doses, these being gradually increased. The use of autoserum, intravenous

LICHEN PLANUS

This is an inflammatory disease of the skin that is usually subacute in its onset, though it tends to run a chronic course and to recur many times after spontaneous recovery or "cure." It is characterized by the appearance, principally on the flexor surfaces of the wrists and forearms and the inner aspects of the knees and thighs, of intensely itching, glistening, red to violaceous, round, angular or star-shaped, plane-topped, pinhead-sized papules; at first these tiny papules, many in number, remain discrete, but they tend ultimately to coalesce into rough scaly patches. The disease not infrequently attacks the visible mucous membranes; other rare forms there are with which we cannot be concerned in this book. Lichen planus is a dry disease throughout its course, with pigmented areas or slightly atrophic spots being sometimes left behind after departure of the lesions. The lichen planus-like malady that occurred in some instances in connection with the quinacrine (atabrine) suppressive treatment of malaria during War II is discussed in the article on Malaria.

THERAPY

Despite the frequency with which this disease is seen in practice, very little advance in its treatment has been made in many years. Most observers feel that "cure" depends mainly on natural evolution and that treatment is therefore principally palliative. However, it is usual to treat the pruritus locally and to give preparations of arsenic and mercury by mouth (the organic arsenicals usually fail when injected) or bismuth by injection; Conrad (1942) favored the use of bismarsen. Some observers feel that the use of iron as in hypochromic anemia is of value especially when combined with the use of arsenic. Burgess (1941) employed preparations containing the vitamin B ... the most stubborn ... variable results, ... vertebrae smacks ... ribed good results ... group of patients, employing an extract made from lichen planus lesions as an antigen; however, since lichen planus varies considerably in its course and tends toward periods of spontaneous remission, a great deal of work will have to be done in confirmation of these findings in order to establish the validity of a type of treatment based upon the rather gratuitous assumption that lichen planus is an infectious disease.

PSORIASIS

... skin ... cal ... and ... and ... ar- ... ite, ... les gray, or silvery imbricated scales. The scraping away of every one from a single papule reveals a very red, easily bleeding elevation, in long-standing cases many of the papular lesions coalesce to form thickened patches

irritants will ultimately get into the eyes when used as long as is necessary in psoriasis. The formula below contains 2 per cent of salicylic acid and 10 per cent of ammoniated mercury; the former may be increased gradually to 5 per cent and the latter very cautiously to 20 per cent; in rare instances both are carried much higher than this (warning. a few instances of severe idiosyncratic reaction to ammoniated mercury have been recorded):

Salicylic acid	gr. xl	2 4
Ammoniated mercury	ʒiij	12 0
White wax	ʒij	8 0
Hydrous wool fat	℥i ʒij	40 0
Petrolatum	℥iv	120 0

Chrysarobin in Ointment.—The drug is undoubtedly effective in more cases than is any other, but it is extremely disagreeable to use as it stains everything brown The stains are only partially removed from linen by the

cautiously increased to 25 or even 35 per cent, though few cases will stand this latter concentration The formula contains 5 per cent:

Chrysarobin	ʒiss	6 0
Petrolatum	℥ij	60 0
Hydrous wool fat to make	℥iv	120 0

formula:

Anthralin	0 1–1 0 per cent
Petrolatum to make.	

be prescribed in any one of these media to be painted on, a method more acceptable to the fastidious patient but less effective than the use in ointment, the gutta-percha formula is to be preferred, as chrysarobin is not soluble in collodion The formulae contain 6 per cent, to be increased just as in the ointment.

Chrysarobin	ʒss	2 0
Collodion (not the flexible) to make	℥i	30 0
Chrysarobin	ʒss	2 0
Solution of gutta-percha (N F IV) to make	℥i	30 0

or the following may be written:

Chrysarobin	ʒij	8 0
Glycerogelatin (N F VIII) to make	℥iv	120 0

utterly without significance in a disease so variable as this. The internal remedies recommended are legion, but the only one to which dermatologists return after their dallyings with other drugs—if they return at all—is arsenic. It is usually begun at 1 to 3 drops of Fowler's solution (U.S.P. solution of potassium arsenite) three times daily, and increased 1 drop per dose every other day until 10 drops are being taken after each meal; this dose is maintained for a week or ten days unless signs of slight poisoning supervene earlier, *i.e.*, puffiness under the eyes or about the ankles, or gastro-intestinal disturbances. *It is not commonly realized that arsenical neuritis* can also be produced with this method of administration. The best practice is perhaps to rest the patient for a while after he has been held the week or ten days on the full dose, but some practitioners gradually reduce the dose and thus bring him back again by gradations to a nonarsenical basis. There is nothing to indicate that [illegible] manganese have both [illegible] irse the latest agents [illegible] vitamins, especially vitamins B, C, D, and P (citrin); there have been some good results of course because psoriasis is capricious and will respond at times to almost anything or again to nothing at all—witness Thurmon's (1942) report of beneficial effect in 62 per cent of seventy-five patients, and Saunders' (1944) report of favorable responses in 55 per cent of twenty-seven patients, given sarsaparilla tablets. *I think the most important recent report is that of Madden (1940),* who treated 112 patients with the following agents: vitamin D, vitamin B_1, vitamin B complex, brewers' yeast, vitamin C, liver extract, diluted hydrochloric acid, estrogenic substance, sulfanilamide, bismuth salicylate, anterior pituitary extract or adrenal cortex extract alone or in combination with one another or in combination with a low-fat diet. No results which one could by any means call impressive came out of this study—Madden's treatment of choice remained a low-fat diet plus vitamin B, and some sort of exfoliating ointment.

A standard treatment is to send the patient south, but he is not *likely to* benefit greatly by a mere sojourn in a warm climate unless the body is freely exposed to the sun.

In the local treatment of psoriasis it is very essential that all the scales be *removed before applying* the remedial agent. This is usually accomplished by vigorous scrubbing with soap and water in a warm alkaline bath, but there are a few individuals who are made worse by the contact with water; for these, [illegible], the scrubbing of the body with [illegible] is then to be thoroughly wiped [illegible]

Hydrous wool fat (lanolin)	℥v	20 0
Glycerite of boroglycerin	℥ij	60 0
Petrolatum to make	℥iv	120 0

[illegible] are perhaps those most used in treatment; the [illegible] n some cases the whole [illegible] ıld be worked into the [illegible] applied to other than diseased areas.

Ammoniated Mercury and Salicylic Acid.—For treatment of the scalp and face a combination of these drugs is employed, as chrysarobin and the other

dilection of this disease are the scalp, the regions about the ears, the cheeks and the bridge of the nose; perhaps the next most frequent site is the back of the hands. The mucous membranes are involved in about one fourth of the [illegible]

The etiology of this malady is entirely unknown. The cases usually begin between the fifteenth and thirtieth years and run an erratic course throughout the rest of the patient's life, though spontaneous disappearance sometimes occurs. There are no constitutional symptoms, and the patient's welfare is disturbed only insofar as the unsightliness of the affliction alters his or her environmental reactions. The acute disseminate variety of the disease, with its severe general symptoms and grave prognosis as to life, is too rare to concern us in this book

SYSTEMIC THERAPY

It is said that rest is very valuable in the control of this disease. In acute exacerbations the patient must be protected from light, oftentimes to the extent of keeping him in total darkness for many days or even weeks The fact that there are several types of systemic therapy indicates, I think, that there is dissatisfaction with them all.

[illegible]

Arthritis (see Index)

Bismuth and Arsenic.—Pillsbury *et al.* (1942) recommended weekly injections of bismuth just as in syphilis, a course of at least eight weekly injections being necessary to determine whether or not the agent would be effective As above stated, Stokes *et al.* (1944) valued bismuth more highly than gold, they stressed the nonspecific quality of the effect since in some instances arsenicals are effective where bismuth fails. Weiss *et al* (1941) reported some success with the use of bismarsen, and both Goldberg (1945) and Hyman (1946) reported good results with mapharsen.

Sulfonamides and Penicillin.—According to Barber (1940), the reactions to sulfonamides are of frequent occurrence in this disease and of peculiar nature and violence. Pillsbury *et al* (1942) did not recommend the sulfonamides in the Military Manual of Dermatology. I have seen no record of the satisfactory employment of penicillin.

Quinine and Iodine.—The patient is given $7\frac{1}{2}$ grains (0.5 gm) of quinine sulfate three times daily for five to seven days, during which time the lesions are painted with a tincture of iodine once each day, after a week, during which the crusts are removed either spontaneously or by poulticing, another course of treatment is given. Stokes *et al* (1944), while not themselves endorsing this treatment, said that it is supported by a number of experienced observers, they said that quinine should be pushed to at least 30 grains (2.0 gm.) a day.

Such a gel is melted and applied with a brush and covered with a bandage. Some *physicians prefer the zinc oxide paste for vehicle:*

Chrysarobin	ʒiss	6.0
Zinc oxide	℥j	30.0
Starch	℥j	30.0
Liquid petrolatum to make	℥iv	120.0

Tar.—The following are forms in which this substance is frequently applied:

Pine tar ointment (U.S.P. XIII)	℥j	30.0
Petrolatum to make	℥iv	120.0
Oil of cade (Juniper Tar, U.S.P. XIII)	℥j	30.0
White wax	ʒij	8.0
Hydrous wool fat	℥j ʒij	40.0
Petrolatum to make	℥iv	120.0

Chrysarobin, Tar and Salicylic Acid.—A compound sometimes successfully used during my time at the New York Skin and Cancer Hospital had the following formula:

Rectified oil of birch tar (N.F. VIII)*	ʒiij	12.0
Salicylic acid	ʒvj	24.0
Chrysarobin	ʒvj	24.0
Anhydrous wool fat	℥j	30.0
Soft soap to make	℥iv	120.0

* In the interest of simplification of our armamentarium, I see no reason why this preparation, the beloved Oleum rusci of the dermatologists, could not in all instances be replaced by the oil of cade, a U.S.P. preparation from which it surely can differ only slightly, if at all, therapeutically.

Coal Tar.—Coal tar is often better borne than the wood tars, it may be substituted in any of the above formulae.

Unna's Chrysarobin-Ichthyol Compound.—This much-used preparation is variously written, but I believe the following formula to be the one most often employed.

Chrysarobin	ʒiss	6.0
Salicylic acid	gr. xlv	3.0
Ichthyol	ʒiss	6.0
Petrolatum to make	℥iv	120.0

Resorcinol.—This drug is used in ointment in the strength of 5 to 10 per cent; the formula contains 5 per cent:

Resorcinol	ʒiss	6.0
Petrolatum	℥ij	60.0
Hydrous wool fat to make	℥iv	120.0

LUPUS ERYTHEMATOSUS

Lupus erythematosus is a chronic inflammatory skin disease characterized by the insidious development of small, pink, dry, macular patches with grayish adherent scales; which patches, both by extension and coalescence, form well- ... *varying in size* from a small coin to the palm of the ... ne large or several small thin, color- ... follicular orifices. The sites of pre-

dilection of this disease are the scalp, the regions about the ears, the cheeks and the bridge of the nose; perhaps the next most frequent site is the back of the hands. The mucous membranes are involved in about one fourth of the

majority of cases these patches resemble no butterfly ever seen or heard of.

The etiology of this malady is entirely unknown. The cases usually begin between the fifteenth and thirtieth years and run an erratic course throughout the rest of the patient's life, though spontaneous disappearance sometimes occurs. There are no constitutional symptoms, and the patient's welfare is disturbed only insofar as the unsightliness of the affliction alters his or her environmental reactions The acute disseminate variety of the disease, with its severe general symptoms and grave prognosis as to life, is too rare to concern us in this book.

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LOCAL THERAPY

Pillsbury et al (1942) made the point that ultraviolet irradiation or roentgen therapy should *never* be employed in this disease. Local destruction of small fixed lesions with solid carbon dioxide snow seems permissible, but as many failures as successes are recorded with this measure. I list below the agents most frequently employed locally but can only say that they have been found one and all to be sadly lacking in ability consistently to produce the kind of results that are occasionally reported following their use.

Sulfur.—This drug is usually applied once or twice daily in ointment; the formula contains 4 per cent, but it may be increased in strength:

Precipitated sulfur	gr. xx	1 2
Petrolatum to make	℥j	30 0

Sulfur and Salicylic Acid.—These drugs are used in combination to be applied in ointment once or twice daily, or alternated with the sulfur alone; the formula contains 4 per cent sulfur and 10 per cent salicylic acid, both of which may be gradually increased:

Precipitated sulfur	gr. xl	6 0
Salicylic acid	ʒiij	12 0
White wax	ʒij	8 0
Hydrous wool fat	℥j ʒij	40 0
Petrolatum to make	℥iv	120.0

Lotio Alba.— I' ... sulfate,
usually applie
of the lotion, .
of the use of this *lotio alba*, see Acne.

Zinc sulfate	ʒij	8 0
Sulfurated potash	ʒij	8 0
Water to make	℥iv	120 0

Ichthyol (Ichthammol).—This drug is applied once or twice daily in ointment or collodion in 10 per cent strength.

Ichthyol	♏xlv	3 0
Petrolatum to make	℥i	30 0

or

Ichthyol	♏xlv	3 0
Collodion (not the flexible) to make	℥i	30 0

Phenol.—Pure liquid phenol is washed over the lesions once a week with a cotton applicator.

Phenol-Lactic Acid.—The following mixture is applied with a glass rod over the surface of the lesions once every ten days to two weeks: phenol, 1 part; lactic acid, 4 parts. The parts should first be cleansed with ether.

Trichloracetic Acid.—This substance is painted on the lesions with a cotton applicator once a week, the parts having first been cleansed with benzine to facilitate penetration.

Arsenic.—Equal parts of arsenic trioxide and acacia are made into a paste with a saturated solution of cocaine hydrochloride and spread over the diseased area, though no more than a square inch at a time should be treated. The paste is allowed to remain in place for twenty-four to forty-eight hours, when the slough is removed by poulticing.

Pyrogallol (Pyrogallic Acid).—This substance is applied in ointment to

Pyrogallol..	.. ʒiss	6 0
Rosin cerate ...	.. ʒiv	15 0
Petrolatum to make	.. ℥i	30 0

ECZEMA-DERMATITIS

There is a large group of maladies characterized histopathologically by an identical process of spongiosis The occurrences are erythema, intercellular epidermal edema, microscopic and later macroscopic vesiculation, with or without the appearance of small isolated subvesicular papules The lesions weep when the vesicles rupture and encrust when the high-fibrin exudate coagulates, scaling occurs if the keratinization process is much interfered with, and continued inflammation causes the skin to lose its elasticity and thicken with exaggeration of the normal lines (lichenification) Dermatologists are intensively seeking to simplify the very puzzling nomenclature of this group, but it seems to me that for the man in general practice who has had no specialized dermatologic training, the most profitable course is to consider any case in which the gross lesions more or less comply with the above description as one belonging in the "eczema-dermatitis" class. All such cases have an identical therapeutic approach; *i e.,* each needs to be investigated from the standpoint of the "general considerations" presented below, and some will require the "local treatment" described farther on

THERAPY

General Considerations

The Metabolic and Endocrine Factors.—It is now apparent after a good

by study of the general functions

The Neurogenic Factor.—These dermatoses rarely heal in persons whose

ber

nes

vas

mycosis may even be influenced by the stock market, and eczema by a course in French "

The Allergic Factor in Adults.—The importance of allergy in the causation

rose, ragweed, hair and fur dyes, inks (the Sunday rotogravure section), face powders, and a host of other domestic and industrial substances are already convicted, as are also a number of foods. Sensitization studies are often very difficult and the manifestations quite fickle in these cases, at one

nomic nervous system to fatigue and irritation, as Stokes asserts, so that a patient who cannot wear a certain fur jacket this season but can do so the next may not be putting us to shame at all but rather showing conclusively how much the allergic state is bound up with other affairs. The reader must turn back and study the subject of allergy, its detection and methods of treatment. The usual injection methods of desensitizing have upon the whole been disappointing in the skin cases; the withholding of convicted foods is much more often rewarded by instant improvement.

restricted, and the ones with acid, green, loose stools will be helped by sugar restriction, but why eczema should be associated with such digestive disturbances, and be relieved when they are corrected, is far from clear. In the vast majority of cases there is no such association and it is here that one might expect the allergic approach to be the most profitable. However, intracutaneous or scratch tests do not offer a very accurate index of clinical sensitivity, for oftentimes identification of the offending substance is not followed by cure of the attack when the substance is withdrawn, or the patient may give a negative test—for example, to cow's milk—and clear up nevertheless when this article is removed from the diet. Some allergists feel that so far as foods are concerned the only thing of value is the ingestion test; Cooke (1944) would

... the "clinical test by trial and error,"
... s in his clinic
... antile eczema
... these children
... ied However,

in some instances there is such a pronounced relationship between food sensitivity and eczema that the mere presence of the food substance in the environment of the infant, even without ingestion, will be productive of violent symptoms; Horesch (1943) reported nine cases in which symptoms were provoked by inhalation of the vapors or odors from the convicted food, either cooked or raw. Hill (1947), to whose critical review of this subject the reader is referred, stressed the hypothesis in explanation of infantile eczema that it is an allergic reaction, the infant becoming primarily sensitized to egg that may reach him either through the placenta in intra-uterine life or through the breast milk after birth; this high degree of sensitization having become fixed in the infant, he tends more easily to become sensitized to other food and environmental

... infantile eczema

tutes in the treatment of milk allergy.

Boiling of Milk.—Many pediatricians have observed that the boiling of milk for four to six hours, or the substitution of evaporated milk, and the prolonged boiling of all foods, are often helpful measures. Ratner (1935), and

supplement the diet and it may be provided in the form of fruit juices if the patient can tolerate them or in the form of ascorbic acid.

Desensitization to Milk—Desensitization to milk was attempted by Ratner, beginning with doses of cow's milk of a drop or less daily by mouth and increasing the quantity so slowly that normal amounts would not be reached until six to nine months had passed Individuals thus desensitized are said to require to take milk continuously throughout their lives to retain the immunity.

Fatty Acids—It is not yet definitely known whether in man, as in several species of lower animals, certain unsaturated fatty acids are essential for the

mix it with sugar, peanut butter, cinnamon or jam, or to serve it with cereal or as a palatable spread In a few cases raw linseed oil or corn oil were substituted for lard Assessing the results in the 148 patients after two or three months of this therapy, it was said that the effects were good to excellent in sixty, and fair to good in fifty-one Several years before the work of Hansen *et al*, Burr (1942) had reported a case that cleared entirely under treatment with two or three teaspoonfuls of lard each day for a month; and in this connection it is interesting to note McLendon's (1945) record of the control of eczema in his own person through many years by ingestion of large amounts of corn, cottonseed and linseed oils, and the eating of many pounds of lard.

Human Dander in Infantile Eczema.—Simon (1944) stated his belief that human dander is important as a cause of eczema in infants and young children,

offering the following evidence: (a) positive skin reactions to the patch test with human dander in fifteen of twenty infants and young children with eczema and only one positive reaction in twenty-three non-eczematous infants and children (might one question these dander patch tests on the basis of histamine content?); (b) the fact that all children are exposed to their own dander or that of others; (c) prompt clinical improvement in three of four cases following the institution of measures directed at avoidance of contact with human dander; (d) reproduction of the lesions at will in four cases (out of four attempts) on a previously uninvolved skin area by exposure of this area to contact with human dander. Simon has since written extensively on this subject, and in conversation with allergists I have gained the impression that they feel there is undoubtedly evidence in many cases of the relationship postulated by Simon, but I have not as yet seen a published report confirming his findings independently.

Focal and Secondary Infection as a Factor.—It is a definite clinical impression that a focus of infection somewhere in the body has a very deleterious influence on eczema-dermatitis. Obviously, every effort should be made to eradicate foci, but bearing in mind the "high-strung" nature of many of these patients, the pursuit of the elusive foe must be made with the utmost calmness and even leisure. In some instances a secondary disease engrafted upon the primary may be the more serious of the two, as was the case in instances reported by Wenner (1944) in which infantile eczema was complicated by the virus of herpes simplex. Boisvert and Powers (1944) said that when a child has eczema and streptococcal fever concomitantly it is likely that the skin lesions will become endogenously infected with hemolytic streptococci. In such instances treatment of the skin lesions with sulfathiazole ointment is often effective but one must always weigh the danger of inducing sulfonamide sensitivity in this way and thus prohibiting subsequent use of the drug when it is urgently needed as a life-saving agent. Pillsbury (1946) said that in his opinion penicillin should not be applied locally in secondarily infected eczema, the parenteral injection being the treatment of choice. Downing *et al.* (1947) reported that in twenty of twenty-six cases of infectious eczematoid dermatitis good to excellent results were obtained through the employment of furacin soluble dressing, the shortest period required for healing being four days and the longest eighteen days with an average of 8.6 days. Treatment consisted in application of the dressing twice daily; temporary irritation was noted in two of the five patients who did not respond to treatment.

Types of Skin.—The person with the dry, ichthyotic, parchment-like skin [illegible] because of the increased sweat-
[illegible] he reason that his type of
[illegible] ema-dermatitis career with
[illegible] soap and to use greases
[illegible] be given
[illegible] glandular
[illegible] endency,
[illegible] hydrates
Stokes feels that there is a definite indication for [illegible] in the dietary, since the process is probably closely bound up with the carbohydrate storage mechanism and metabolism in the skin In these cases the scalp, which is always concerned in the seborrheic process, must be treated; sulfur will be found to be almost specific when properly used; and there is a

definite indication for the use of the roentgen ray to reduce the activity of the sebaceous glands. Prognosis is better than in the ichthyotic type.

A good ointment for use after the bath by persons with excessively dry skin is the following:

Hydrous wool fat	℥ v	20.0
Glycerite of boroglycerin	℥ ij	60 0
Petrolatum to make	℥ iv	120 0

As a substitute for soap, Lane and Blank (1941) offered a mixture that I present in prescription form below:

℞ Sulfonated olive oil	℥ ij	60 0
Sulfonated teaseed oil	℥ ij	60 0
Liquid petrolatum	℥ iv	120 0
Water to make	O j	500 0
Label Use as soap substitute		

Mycotic Factor.—With regard to the mycotic factor, it can only be said that undoubtedly many cases of so-called "epidermophytosis" are really eczema-dermatitis, and conversely that some cases of eczema-dermatitis have a mycotic factor uppermost Certainly many cases of epidermophytosis that are resistant to the ordinary treatment will be found upon careful re-study to have become eczematous, particularly beyond the borders of the original mycotic infection, and are being aggravated perhaps by the application of strong keratolytics

Local Treatment

Early Stage.—In the vesicular stage the use of wet dressings is the method [illegible]

follows:

Potassium permanganate (1 tablet)	gr v	0 3
Water to make	3 quarts	3000 0
This is an approximately 1 9000 solution		

Of course saturated solution of boric acid may also be used, but the permanganate solution is not apt to become excessively irritating if inadvertently [illegible]

[illegible]

[illegible]

oatmeal, *and squeeze it in the bath until* the water becomes opalescent. Such baths may be taken for ten to twenty minutes several times daily. Afterward the patient is to be patted dry and may have the official rose water ointment lightly applied; or the body may be powdered. In some patients, 1 quart (1 liter) of vinegar to the tub of water has antipruritic effect.

Some patients do not bear wet dressings well and must be treated with such lotions as will coat the lesions, or perhaps even with powders. The N.F. calamine lotion coats well but will crust if allowed *to dry too much between applications*; it is to be removed with sweet oil, not water, or with the oil and egg-[illegible] into the skin and then [illegible] for twenty or thirty [illegible] emulsion; the addi*tion of a few drops of water helps. Rinse in cool* water. *In some* patients the amount of inert powder in the calamine lotion makes it too drying and irritating, but they will often find a mixture of the lotion and sweet oil in equal parts very soothing.

Prepared calamine	℥j ʒiss	40.0
Zinc oxide	℥j ʒiss	40.0
Glycerin	ʒiiss	10.0
Magma of bentonite	℥vi ʒv	200.0
Solution of calcium hydroxide to make	Oj	500.0

Note should be taken of Goodman's (1945) statement that zinc oxide may be substituted for calamine, which is merely zinc oxide plus some iron rust, in all formulas for use on the skin. A simple powder for dusting on dry or wet lesions is the following:

Zinc oxide	℥j ʒiss	40.0
Talcum to make	℥iv	120.0

The addition of 2 drachms (8 gm.) of salicylic acid will make the powder antiseptic, but of course such a mixture must be used *with extreme caution on* acutely inflammed lesions. Menthol, with talcum to make it stick, is often remarkably antipruritic:

Menthol	gr. xl	2.5
Talcum to make	℥iv	120.0

Sometimes before using such a powder it is of advantage to sponge the affected area with hot sodium bicarbonate solution and then apply the powder after merely mopping off the solution.

For more active antipruritic effect, 1 to 2 per cent each of phenol and menthol may be added to the calamine *lotion, but of* course open or very acutely inflamed lesions contraindicate this application.

In some acute cases, particularly of infantile eczema-dermatitis, crude coal tar ointment may be used from the very beginning:

Crude coal tar	ʒss	2.0
Zinc oxide	ʒss	2.0
Petrolatum	℥j	30.0

Since the above preparation is often removed *from the surface* of the body with great difficulty, Downing *et al.* (1944) suggested as a substitute for the petrolatum *a special base* consisting of 5 per cent of diglycol stearate and 95 per cent of petrolatum prepared by fusing these two substances together and

In cases of infantile eczema it is nearly always necessary to resort to forceful prevention of scratching, either through tying the wrists and ankles loosely to the sides of the crib or resorting to the employment of splints. A light masturbation splint, applied just above the knees, will effectively prevent rubbing with the feet. Wool should not come in contact with the body, and in some cases it is best to dress only in a diaper in a draped crib with an electric bulb to keep it warm Pilcher wrote as follows of epinephrine to relieve the excessive itching: "The hypodermic dose was from 0.1 to 0.3 cc. of the 1:1000 solution, seldom more than 0 2 cc., however. This is somewhat large in comparison with the usual adult dose, but harmful effects were not seen. Occasionally pallor of the face and extremities (from vasoconstriction) was noted, of but a few minutes' duration without other signs of toxicity. It is my impression that the relatively large dose is necessary for effective results The infants varied somewhat in their reaction to epinephrine; for instance, one of 9 kg. weight was relieved of its suffering with 0 15 cc. and became quite pale with 0.2 cc., while a 5.5 kg infant of about the same age required 0 2 cc for results and showed pallor only with 0.3 cc. The relief is usually striking, is noted promptly, often within two minutes, just as it is in urticaria, and may persist for an hour or more, and not infrequently the patient falls into a restful sleep."

Subacute Stage.—After the more acute symptoms have subsided, the use of creamy pastes and salves may be begun, either for protection from clothing and dirt in the milder cases, or to tide over the period of subsiding inflammation in those cases in which it is apparent that the use of stronger stimulating and keratolytic agents will be later necessary. They are spread over the lesions like butter. Unna's soft zinc paste is much used.

Zinc oxide	℥j	30 0
Precipitated calcium carbonate	℥j	30 0
Linseed oil	℥j	30 0
Solution of calcium hydroxide	℥j	30 0

Lassar's zinc paste has a small amount of salicylic acid (2 per cent), which is slightly stimulating, and it is of such consistency that, if hydrous wool fat is substituted for half the petrolatum, a liberal dusting with talcum powder will form a crust on top of the application that requires little further protection from the clothing

Salicylic acid	gr xl	2.5
Zinc oxide	℥j	30 0
Starch	℥j	30 0
Petrolatum	℥ij	60 0

Another well-know paste is that of Boeck:

Glycerin	ʒiij	12 0
Starch	ʒvj	24 0
Talcum	ʒvj	24 0
Solution of lead subacetate to make	℥iv	120 0

Some observers of large experience like to use ichthyol (ichthammol) in this stage. Becker (1917) favors the following, in which the ichthyol is present only

to the extent of approximately 3 per cent; it is his feeling that most physicians apply ointments that are too strong and that this 3 per cent ichthyol ointment is effective in most instances because it is mild, vasoconstrictive and antipruritic.

Ichthyol	ʒj	4 0
Zinc oxide	℥j	30 0
Petrolatum to make	℥iv	120 0

In using any of these pastes or salves, water should not be employed for their removal; use sweet oil, or the method of Glaze (described in the beginning of the section on local treatment).

Chronic Stage.—Before applying any of the stimulating and keratolytic agents in effective strength, it is good practice to try out the sensitiveness of the skin with a very mild stimulant; for instance, the ichthyol-zinc paste above, or one can proceed to the use of salicylic acid and the tars by first applying the following, in which each of the active ingredients is present only to the extent of 0 5 per cent (therefore, doubling these two figures would give 1 per cent, tripling 1 5 per cent, quadrupling 2 per cent, etc.):

Salicylic acid	gr iss	0 15
Pine tar	gr. iss	0.15
Zinc oxide.	ʒij	8 00
Petrolatum to make	℥j	30 00

The best of the available tar preparations are pine tar, coal tar, and juniper tar (oil of cade). For any of them dosage must be determined in each individual case; as previously stated, coal tar is often surprisingly well borne in high concentration. Juniper tar has perhaps the least unpleasant odor, but all of [illegible] few pages back is a [illegible]

Sulfur may also be used in any proportion if the patient's tolerance is first carefully tested, the seborrheic greasy type will bear it best and derive the most benefit from it. In the following, 3 per cent is combined with 1 per cent of salicyic acid, and an ointment instead of paste base is used.

Precipitated sulfur.	ʒss	2 0
Salicylic acid	gr x	0 6
White wax.	ʒj	4 0
Hydrous wool fat	ʒv	20 0
Petrolatum to make	℥ij	60 0

If greater cerate-like consistency is desired, paraffin may replace the wool fat and be increased up to 50 per cent

Resorcinol concentration must also be *gauged by* each patient's individual reaction; it is best perhaps to begin with 1 or 2 per cent, but less than 5 per cent is rarely effective on thickened areas, it is occasionally carried up to 20 per cent. The formula contains *5 per cent:*

Resorcinol.	gr xlv	3 0
White wax	ʒj	4 0
Hydrous wool fat	ʒv	20 0
Petrolatum to make	℥ij	60 0

For more prolonged application, the paste base would be substituted.

Ammoniated mercury is also very useful at times; in the following, 5 per cent is combined with 20 per cent of the liquid tar preparation of the N.F.:

Ammoniated mercury	gr xlv	3.0
Solution of coal tar	ʒiij	12.0
Hydrous wool fat	℥j	30.0
Petrolatum to make	℥ij	60.0

There is twice as much wool fat as petrolatum here because of the necessity to incorporate the large amount of fluid; the anhydrous fat would be even better.

Local treatment of some sort is necessary in practically all cases of eczema-dermatitis, but it is by no means certain that in a given case the same preparation will be serviceable for all lesions. At times acute weeping areas on one portion of the body will demand wet dressings while lichenified areas elsewhere are being treated with the tars, salicylic acid, and so on. Utmost co-operation on the part of the patient is of prime importance.

Special Antidotal Measures in Ivy Poisoning

Ivy poisoning is a serious matter and I do not feel warranted in omitting the special measures that have been employed in combating it, but as a result of an attempted evaluation of such measures, Howell (1943) concluded that under the circumstances in which they are likely to be employed, practically none of them is effective, indeed, the fact that so many agents are listed [illegible]

the object is to get rid of the irritant, therefore the soaping and rinsing must be done in the direction away from the unaffected parts, *i e.*, wash from the elbows down toward the hands and rinse in the same way. If the area is then rinsed or wiped over with alcohol, which is a solvent for the poison, this too must be done in the direction away from the unaffected skin Gasoline also is a solvent to be used in the same way. Park (1945) has said that if an early case of ivy poisoning is treated by the application of water as hot as can be borne without scalding, it can be immediately stopped from itching and will dry and frequently not even need a second treatment.

Lead.—Lead preparations, such as the lead and opium wash of the N.F. (lead acetate, 18 gm, tincture of opium, 35 cc., water to make 1000 cc.), are not so popular now as formerly, at best they merely precipitate the poison, which must then be washed away.

Sodium Sulfite and Phenol.—Sutton said that a saturated solution of sodium sulfite, to which 0.5 per cent phenol has been added, served him well; the following should be written:

Exsiccated sodium sulfite (U S P. IX)	℥viij	250.0
Phenol	ʒj gr xv	5.0
Water to make	Oij	1000.0

Formaldehyde and Phenol.—Hessler some years ago described his formula [illegible]

to the extent of approximately 3 per cent; it is his feeling that most physicians apply ointments that are too strong and that this 3 per cent ichthyol ointment is effective in most instances because it is mild, vasoconstrictive and antipruritic.

Ichthyol	ʒj	4.0
Zinc oxide	℥j	30.0
Petrolatum to make	℥iv	120.0

In using any of these pastes or salves, water should not be employed for their removal; use sweet oil, or the method of Glaze (described in the beginning of the section on local treatment).

Chronic Stage.—Before applying any of the stimulating and keratolytic agents in effective strength, it is good practice to try out the sensitiveness of the skin with a very mild stimulant; *for instance, the ichthyol-zinc paste* above, or one can proceed to the use of salicylic acid and the tars by first [illegible] is present only [illegible] ures would give [illegible]

Salicylic acid	gr. iss	0.15
Pine tar	gr. iss	0.15
Zinc oxide	ʒij	8.00
Petrolatum to make	℥j	30.00

The best of the available tar preparations are pine tar, coal tar, and juniper tar (oil of cade). For any of them dosage must be determined in each individual case; as previously stated, coal tar is often surprisingly well borne in high concentration. Juniper tar has perhaps the least unpleasant odor, but all of [illegible] a few pages back is a [illegible]

Sulfur may also be used in any proportion if the patient's tolerance is first carefully tested, the seborrheic greasy type will bear it best and derive the most benefit from it. In the following, 3 per cent is combined with 1 per cent of salicyic acid, and an ointment instead of paste base is used.

Precipitated sulfur	ʒss	2.0
Salicylic acid	gr. x	0.6
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

If greater cerate-like consistency is desired, paraffin may replace the wool fat and be increased up to 50 per cent.

Resorcinol concentration must also be gauged by each patient's individual reaction; it is best perhaps to begin with 1 or 2 per cent, but less than 5 per cent is rarely effective on thickened areas; it is occasionally carried up to 20 per cent. The formula contains 5 per cent:

Resorcinol	gr. xlv	3.0
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

For more prolonged application, the paste base would be substituted.

crusts, though healing will nevertheless be complete in a few days The spraying itself was said to be relatively painless, the first sensation being that of cold and then that of burning, and finally that of numbness Robinson suggested that in spraying lesions on the face the nose be clamped and the patient caused to breath through a tube to avoid general anesthesia.

Desensitization Against Poison Ivy.—It seems to me that the statement of Sulzberger *et al.* (1946) expresses the consensus with regard to the use of poison ivy extracts, to wit "Specific desensitizing procedures are generally conceded to be ineffective in preventing most types of eczematous dermatitis from external contact" Stevens (1945), reviewing the entire matter for the Council on Pharmacy and Chemistry, said that since there is no controlled statistical evidence that the daily ingestion of small amounts of extract over a

with repeated doses of extract begun well before the season and increased in strength at frequent intervals within the tolerance of the patient I suppose the best that the practitioner can do at the present time is to follow the directions on the package

BOILS

(Furunculosis)

Boils are acute, deep-seated, circumscribed inflammations of sebaceoous glands or hair follicles, the causative organism is probably a staphylococcus in most instances In the beginning the skin is smooth, tense and red, but in a few days the head of the elevation either becomes pustular or the whole mass becomes boggy, at this point the boil either discharges its pus and necrotic tissue or retrogresses without rupture. There may be a great many boils present at one time on various portions of the body surface, and in some cases new "crops" continue to appear for many months The individual lesions are very painful and the patient
seldom dangerous to life exc
are on the face or upper lip.
acute infectious disease is a very serious matter

THERAPY

Penicillin.—The use of penicillin parenterally in the treatment of boils is usually successful in controlling the infection, but the necessity of injecting the patient at frequent intervals around the clock has seemed an excessively

directing the point of the needle to the center of the base of the lesion, and injecting 0 5 to 1.0 cc of the penicillin solution. If the furuncle was at the stage

essential oil may be added). In dispensing I supply a 4-*drachm vial* with swab in the cork and with the directions: Apply freely the first time; afte that use *sparingly every few* hours as needed. . . .The hardening and tannin effect of formaldehyde must be *considered* and explained to patients. Th earlier the solution is applied, the better the effect."

Zinc Sulfate.—Irving *wrote enthusiastically* of the use of zinc sulfate "All irritation and even eruption can be *prevented if it* is used immediatel after exposure If used within twenty-four hours after *exposure or ten hour* after the appearance of the vesicles, it will abort the attack. If *the case i* not seen until the deeper layers of the epidermis are involved, the *cure i* slower but just as sure. To abort an attack, use 10 grains (0.6 *gm.*) *of zin* sulfate to 1 ounce (30 cc.) of water. For later treatment, use half *strength.*"

Ferric Chloride and Paraffin.—*This* treatment has periods of popularity but *it* should not be used because it may cause permanent pigmentation. Traub (1947) said that if the action has been only superficial the "tattooing" *may be removed* by peeling the skin with a cold quartz lamp or with chemicals, *but that in most cases that he has seen the pigment has been at such a depth* that it has been impossible to remove it.

Benzoyl Peroxide.—Lamson stated that very great relief follows upon the application to the lesions of benzoyl peroxide as a dusting powder in a considerable proportion of cases, but pointed out the inadvisability of using the substance in this form because of its high inflammability and explosiveness. A paste made from the powder and a lubricating jelly containing glycerin was said by him to be just about as effective and to be nonexplosive and no more inflammable than a bandage.

Tannic Acid.—Schwartz and Warren (1941) reported the successful use of this agent in a small number of cases: vesicles are clipped open with sterile scissors, or the smaller ones rubbed open with alcohol-saturated gauze, and a dressing soaked in 10 per cent tannic acid solution applied for one-half hour once daily.

Collodion.—Woodward (1940) reported that painting collodion over the [illegible]

[illegible] 1943) found in experimental studies [illegible]

first approach.

Ethyl Chloride.—Robinson (1947) reported that only five of ninety-six cases treated by spraying the lesions with ethyl chloride failed to respond well The ethyl chloride is sprayed on the involved areas until the skin begins to frost, and then continued for a few additional seconds until the sprayed area is hard to the touch. The sprayings are repeated at twenty-four hour intervals and a case is considered cured when all the vesicles have ruptured, the vesicular fluid has been absorbed, no oozing is present, and the infected area is dry. Robinson said that twenty-four hours after spraying the lesions one will note that the area becomes intensely red, that some of the vesicles are ruptured *and their* contents congealed, and that other vesicles are absorbed; no attempt should be made at any time to remove the crusts or the remains of the vesicles, for as the skin heals the crusts and scales gradually fall of. After three or four sprayings the lesions are said to look almost as bad as they did at first because of the

and quickly relieved, and that is of course something Ultrashort-wave diathermy was having a great vogue a few years ago, it seems to me one does not hear it mentioned in this connection quite so often nowadays.

Thyroid Therapy.—Barnes (1943) reported sixteen patients each of whom had a low basal metabolic rate or basal temperature, further lesions did not develop in any of these individuals after the institution of thyroid therapy as in the treatment of myxedema but they did recur when the medication was discontinued

ACNE

Acne is an inflammatory skin disease symmetrically involving the face; sometimes, also, the interscapular or sternal regions are involved, and occasionally the whole back. The skin is greasy, contains many blackheads (comedones), and the acne lesions, which are at first papular, then become pustular, and finally dry up with more or less crusting The essential process in the disease is a functional overactivity of the sebaceous glands, combined with a

individual past twenty-five should cause the physician to inquire into the occupation (tar, oils, paraffin, chlorine), search for foci of infection and question regarding the use of goiter preventives

The consensus is that the ingestion of iodine, even in the small amounts contained in iodized table salt, causes an increase in the number and severity of the lesions, but there are a few men of experience who disagree with this opinion. It was found during War II that acne is much aggravated in the tropics. It is said that the malady is of rare occurrence among such primitive peoples as the Eskimos, native black Africans, Australian aborigines and Maoris, but that as these people adopt modern methods of living the condition occurs more frequently.

THERAPY

General Measures.—The acne patient should be given a thorough physical examination, and especially should a careful history of past ailments be taken, for the elimination of chronic foci of infection has occasionally been rewarded by rapid improvement Usually, however, the malady responds all too slowly to any type of treatment. Here, as everywhere else, I am opposed to the routine employment of drugs "to keep the bowels open" unless constipation is actually shown to exist—and even then cathartics are rarely indicated (see Colon Consciousness). Startin's mixture is used in nearly every case at some time, very likely it has no more value than accrues from giving the patient something to take from a bottle

Startin's mixture

℞	Ferrous sulfate	ʒi	4 0
	Dilute sulfuric acid (U.S P)	℥iv	15 0
	Magnesium sulfate	ʒi	30 0
	Syrup of ginger	ʒi	30 0
	Water to make	ʒiv	120 0

Label 1 teaspoonful after meals and upon retiring, or 4 teaspoonfuls before breakfast.

of pointing, it was said that the increased pressure would frequently cause the top to rupture and the injected fluid could be seen emitting from the opening together with a varying amount of exudate. The needle was then withdrawn.

[illegible]

small, dry, sterile piece of gauze was the only dressing applied. Liles said that under this type of treatment a furuncle of average size usually showed marked regression in twenty-four to forty-eight hours and that often at the end of seventy-two hours it was difficult to find any trace of it except for a very small pit in the skin. However, if marked regression was not shown within one day a similar injection was made on the second day; it was seldom necessary to inject more than twice Liles said that lesions injected at an early stage seldom came to a point and as a rule disappeared rapidly. Rose and Hurwitz (1946) reported treatment of a few boils successfully in this same manner.

Other Local Therapy.—Price (1944) stated that in several instances he [illegible]

no boils present. To hasten maturation, in order that the contents may be evacuate [illegible]

times of [illegible]

developn [illegible]

sugar, bacon, bread and milk, or the whatnots of household medicine) has no advantage over plain water beyond the requiring *of less attention after it is* [illegible]

by contact and also protect any small pimples that might be present [illegible] abrasion and consequent greater likelihood of infection. Underclothing and bedclothing should be changed daily.

Incision.—It is usual practice to freeze the skin over the boil with *ethyl* [illegible]

nward.

e force

ver the

ne pain

nd not

has always been caused by the knife pressure on the [illegible] by the cutting."

[illegible] There are many enthusiastic reports of the results of x-ray [illegible]

Hospitals, reported that twenty-five of thirty [illegible]

Sulfur	7 5
Sodium mixed alkyl benzene sulfonate	110 0
Antipyrine	54 0
Triethanolamine	100 0
Propylene glycol	560 0
Water to make	1000 0

It is believed that the sulfur is carried in this intraderm vehicle through the pilosebaceous apparatus from the outside into the derma and into the epidermis. The patient applies this preparation night and morning, massaging it into the skin with a glass highball stirring rod for one to two minutes, preceding the application by soap and water washing In the morning it is allowed to remain on fifteen minutes and then removed with a towel and in the evening it is left on overnight

solid carbon dioxide and to add one drachm (4 gm) of precipitated sulfur. This is thoroughly mixed and then ethyl acetate is slowly added until a semi-dry slush is formed The consistency may vary according to individual desires and the progress of treatment, a thinner mixture being used early in the treatment because the reaction is not so severe as when thicker mixtures are used. The slush is applied with the grinding end of the pestle to which several layers of gauze have been attached by means of an elastic band. It is recommended that no moisture be allowed to contaminate the ethyl acetate in order to prevent its slow decomposition and acquisition of an acid reaction. Zugerman reported no unfavorable reactions directly traceable to the use of this slush, but it seems to me that this therapy should be left to dermatologists; in communications to me in early 1947, both Dobes and Karp subscribed to that opinion, but Karp said that several dermatologists with whom he is associated

amount of this mixture is massaged into the face for a few minutes three times daily and then rinsed off with water, the frequency of the cleansing being decreased as the skin becomes less oily—indeed, a reduction in the oiliness of

There is certainly less belief today than there was a few years ago in the excessive use of carbohydrates, especially "sweets," as important in prolonging the siege; Crawford and Swartz (1936), who deliberately maintained patients on a high carbohydrate regimen, failed to find the diet in the least harmful. LeWinn and Zugerman (1942) found fat tolerance to be normal in their twenty patients Obviously the "insulin treatment" of acne about which the word went around a few years ago, has come to nothing since there have been no recent reports In 1947, Cormia kindly informed me that he still feels the food allergy [illegible]
a number of ye[illegible]
products and th[illegible]
yeast has died t[illegible]
with the employment of penicillin in twenty-three cases of pustular or cystic acne in the hope of controlling a secondary infection were certainly not brilliant. Ross and Richeson's (1947) results with autohemotherapy in a small series of cases they thought justified them in making a preliminary report; blood was withdrawn from a cubital vein and immediately reinjected into the buttock, the first injection being of 5 cc. and all subsequent ones of 10 cc., and a course consisting of two injections a week for a total of ten injections.

Local Treatment.—The things necessary are to get rid of the blackheads, cleanse and disinfect the skin as much as possible, and apply a keratolytic [illegible]

of the compound solution of cresol has been added to the pint, and then the keratolytic should be applied. At the New York Skin and Cancer Hospital it was formerly, and probably still is, despite the new name for the hospital, the custom to write for *lotio alba* in strengths designated as "2-ply," "4-ply" and "6-ply." The formula below is for the 2-ply lotion, the 4- and 6-ply were obtained by keeping the total quantity of the lotion constant but doubling and trebling the 2 active ingredients:

Zinc sulfate	ʒij	8 0
Sulfurated potash	ʒij	8 0
Water to make	℥iv	120 0

This is to be applied at night and washed off in the morning with hot water and some such gritty soap as hand sapolio; it has also been recommended that potassium nitrate be added to the water in the proportions of 30 grains (2 gm) to the pint (500 cc). After drying, talcum powder, to which has been added 1 drachm (4 gm.) of sulfur to the ounce (30 cc.), should be freely dusted on. This treatment, because of its violence, has frequently to be interrupted by periods during which only cold cream is used at night and calamine lotion during the day.

MacKee *et al* (1945) found the preparation they called "intraderm sulfur" valuable in the treatment of all types of acne; indeed they said the per[illegible] and the length of time required for cure with it compared [illegible]

Arsenic—This drug is usually applied to the form of Fowler's solution (U S.P. solution of potassium arsenite), first softening the lesions by the use of a 5 per cent solution of potassium hydroxide A modified Marsden paste (Hare) may also be applied if the warts are few:

Arsenic trioxide	gr lxxv	5 0
Acacia	gr lxxv	5 0
Cocaine hydrochloride	gr xxx	2 0
Glycerin	♏ xxx	2 0
Water to make a paste		

when it has corroded deeply enough Both dichloracetic acid and trichloracetic acid (the latter much less expensive) are applied in liquid form with a glass rod.

Vleminckx's Solution.—This, the solution of sulfurated lime of the N.F., was often used by Pusey, who employed a small dressing saturated with the solution to the wart overnight and repeated these nightly dressings until irritation was produced; then the treatment was used less frequently until the wart disappeared or until, in cases of plantar warts, the desiccated horny mass could be dug out.

Urea—MacKay (1940) found the injection at the base of the wart of 0 1 to 0 2 cc of 50 per cent urea solution to be useful in about half of a very small series of patients, in 1947, MacKay kindly informed me that other physicians had also used this treatment successfully, though plantar warts have usually been found the most resistant

Formalin—Thomson (1943) recorded the successful treatment of thirty-nine cases of plantar warts in three to four weeks by soaking them nightly for ten minutes in 3 per cent formalin solution, the affected part of the sole was placed in the solution in a small saucer so that the thin skin on the top and sides of the foot did not become wetted

Podophyllin.—Culp *et al.* (1944) reported the successful treatment of condyloma

of 100

twenty-

forty-eight of their fifty patients The latter reporters prepared a 25 per cent

adjacent normal foreskin, it is possible to minimize such contact by wiping away the excess with a dry, clean applicator after the verrucae have been thoroughly covered The material is allowed to remain in contact for only

X-Ray.—Pillsbury *et al.* (1942) in the Military Manual of Dermatology stated that superficial x-ray in safe dosage, administered only by specially qualified persons, is the best of all acne treatments—that indeed it accounts

WARTS

Warts, as is well known, are seen principally in children, but they may develop for the first time in adults. The most frequently encountered types are: the small, flat, so-called "juvenile" warts, occurring principally on the face and backs of the hands; the larger excrescences, known as verruca vulgaris,

verrucae known as condylomata acuminata. It is now believed that warts are caused by a filtrable virus; they seem to be auto-inoculable.

THERAPY

Local Treatment.—Perhaps the most valuable method employed at the present time is fulguration; the lesions turn black and drop off several days after treatment The use of x-rays is often enthusiastically lauded, and recently radium has been also; doubtless the results are excellent in most cases, but it *seems to me that warts are very benign affairs in which to use these potent* and dangerous agents; certainly only skilled dermatologic radiologists should

nitrate are quite effective: the site is frozen with the ethyl chloride

very tedious

Salicylic Acid.

℞	Salicylic acid	ʒiss	6.0
	Collodion	℥j	30.0
	Label. Touch the wart two or three times daily with the solution, having previously removed the adherent collodion.		
℞	Salicylic acid	ʒiss	6.0
	Chloral hydrate	ʒiiss	10.0
	Collodion	℥j	30.0
	Label As above		
℞	Salicylic acid	ʒiss	6.0
	Mercurous chloride	gr xv	1.0
	Hydrous wool fat	ʒv	20.0
	Label Apply to wart several times daily		

THERAPY

Local Treatment.—In most cases the only indication is to protect the lesions from traumatism and subsequent infection For this purpose it usually suffices to apply a dusting powder of thymol iodide and cover the parts with cotton

of the nerve backward toward the cord; it is recommended that the current

mine per cc. into and beneath the areas involved in the eruption, and in 1947 he kindly informed me that after a comparative trial with a number of other measures in a small series of cases he still feels that these injections give him best and quickest results from the standpoint of the relief of pain. There have been a number of reports of the successful employment of x-ray therapy over the spinal root ganglia of the nerves involved—for example, McCombs *et al* (1940) felt that they were successful in checking the pain in thirty-nine of the forty-four patients who began treatment within the first seven days of the

thetic ganglia in four cases, the results were excellent both in relief of pain and promotion of involution of the lesions. Lovell (1946) had similar results in his two cases The latter author very wisely reminds us that it is well to give barbiturates before injecting procaine. Apparently this treatment is an excellent one in the hands of those competent to perform these sympathetic blocks, but it is difficult to understand how the injection of only a small amount of

the abolishing of segmental arteriolar vasospasm, but Rosenak (1947), who perhaps performed the earliest injections, felt it rather likely that the procaine somehow directly influences the virus in the sympathetic and spinal nerve trunks; in substantiation of this viewpoint he emphasized the fact that the paravertebral block is most dramatic in its effects when given within the first three days of the herpes attack, and that the greater the lapse of time between the beginning of the disease and the injection, the poorer and the more uncertain the results, he made the further point that the aged do not respond as well to this treatment as the young and reasoned that perhaps in elderly people, who are not so sensitive to pain as younger individuals, the disease

can of course be had, but codeine sometimes does not suffice and the objections to the prolonged use of morphine or dilaudid, or even demerol, are obvious. McDowell (1941) reported prompt and complete relief following the employment of cobra venom in six cases, which is unusual since such relief as accom-

Treatment by Suggestion.—In Kentucky, in my childhood, the method was to rub the cut side of a potato on the wart, bury the potato and wait: I do not recall the results A bit further west, in the land of Tom Sawyer, there was something about a bloody bean and a cat in the graveyard at midnight, if memory serves me correctly. The practice in Timbuctoo is not known to

have reported in the same vein. I wonder if this advances us very much?

HERPES ZOSTER

(Shingles)

Herpes zoster is an acute inflammatory skin disease characterized by the appearance of crops of vesicles seated upon erythematous bases along the course of one or more of the peripheral sensory nerves, the sites of predilection being the thoracic, lumbar, brachial and supra-orbital regions. In the average case the lesions dry into crusts and disappear in a week or two with little or no accompanying pain, but in severe cases there may be many successive crops of vesicles that persist for a long time and become pustular, rarely even gangrenous; pain of neuralgic character is usually severe in these cases, and in the elderly there is often much pain though the eruption be slight. The disease, which may occur at all ages but is very rare in infancy, is now generally conceded to be a transmissible virus infection of the posterior roots, the ganglia or paraganglionic tissues, with secondary manifestations in the skin. The contention that herpes is an atypical form of chickenpox still remains to be substantiated. So few cases have come to autopsy that the pathology still remains somewhat obscure; reviewing the literature and reporting a case of their own, Krumholz and Luhan (1945) felt uncertain that encephalitis occurs as a complication of the disease, but McCormick's (1947) patient certainly had herpes at least in association with encephalitis, and in Madonick's (1946) case the onset of the nervous complications appeared eight days after the patient was vaccinated as a form of treatment for the herpes, it being Madonick's opinion that the herpes virus likely was activated into a full-blown meningoencephalitis by the vaccinia virus Gordon and Tucker (1945) reported three interesting cases of lesions of the central nervous system in herpes zoster: in one case there was involvement of the lower motor neurons, the second and

zoster appeared after an injury in the region affected by the zoster, the patients symptoms of sensory disturbance having intervened between injury and the outbreak of zoster, and in others not. Klauder referred to a considerable number of other reports of this type of case in the earlier European literature.

Gais and Abrahamson (1939) stressed the difficulty of differentiating herpes before the eruption from certain intrathoracic and intra-abdominal lesions.

Hot Water.—In the article on Eczema, the effect of intense heat in relieving the itching of poison ivy dermatitis is pointed out, and at this present place I call attention to Shaine's (1945) report that he had completely relieved the itching of an allergic pruritus for long periods of time through soaking the feet in extremely hot water. Perhaps the application of extremely hot packs for ten to fifteen minutes upon retiring would aid some patients with pruritus ani to get to sleep

Antipruritic Lotions and Ointments.—I am providing a long list of formulae so that the patient may be switched from one to the other:

Yellow mercuric oxide	gr xx	1.2
Hydrous wool fat	℥ij	60.0
Petrolatum to make	℥iv	120.0
Ammoniated mercury	gr xl	2.4
Hydrous wool fat	℥ij	60.0
Petrolatum to make	℥iv	120.0
Crude coal tar	ʒiij	12.0
Zinc oxide	ʒiij	12.0
Petrolatum to make	℥iv	120.0
The amount of coal tar contained here, 10 per cent, may be much increased		
Phenol	gr. xl	2.4
Zinc oxide	ʒiij	12.0
Ointment of rose water (U S P) to make	℥iv	120.0
Phenol	♏xx–xl	1.2–2.4
Menthol	gr. xx–xl	1.2–2.4
Ammoniated mercury ointment (U S P)	℥j	30.0
Zinc oxide	℥j	30.0
Anhydrous wool fat	℥ij	60.0
Lime water to saturate and make ointment		
Ethyl aminobenzoate (benzocaine)	ʒiij	12.0
Salicylic acid	gr xlv	3.0
Hydrous wool fat to make	℥iv	120.0
Benzyl alcohol	ʒiss	6.0
Hydrous wool fat to make	℥ij	60.0

Injection Therapy.—Since 1916, when Stone introduced perianal injection methods, many solutions have been used with varying success: alcohol, dilute hydrochloric acid, phenol, etc Gabriel's formula, introduced by him [illegible]

0.5 per cent, benzyl alcohol, 10 per cent, and phenol, 1 per cent in sterilized sweet almond oil. With this mixture it is said that anesthesia generally persists for two to six weeks, there is no pain in the injection itself except the first prick of the needle, there is very little likelihood of sloughing occurring, no systemic reactions, and a procedure simple enough that it can be employed in the office Some years ago, Steinberg reported that fifty-one of 100 patients injected had had no recurrences in a two-year period; in 1947, he kindly informed me that 20 per cent of these patients had minor recurrences over a ten-year period but that all had been successfully reinjected. Swinton (1947) said he had obtained temporary relief in all patients in whom he had employed the injection technic.

Steinberg's technic follows:

panies the employment of this agent in other painful conditions usually is very tardy in making its appearance. Some years ago Sidlick (1930) reported that most of his fifty-four patients given intramuscular injections of 0 5 to 1 cc. of pituitrin at twenty-four hour intervals were relieved after only a few such injections; Sulzberger and Wolf (1942) considered this the most effective form of treatment. [illegible] contraindicate [illegible] disease and p [illegible] absence of these conditions. Ruggles (1931) gave intravenously a 20 cc. solution of 30 grains (2 gm.) of sodium iodide on the first, second, fourth and seventh days in fifteen cases, all the patients having been greatly relieved, some not even requiring a full course. Several others have reported favorably upon this iodide treatment, and Sulzberger and Wolf (1942) considered it second in value only to pituitrin, but they warned against iodine intoxication, iodine allergy and iododerma. Walker and Walker (1938) reported relief from pain in cases involving the eyes and forehead and side of the nose following injection of 5000 units of diphtheria antitoxin; I cannot imagine how one would justify such treatment on rational grounds, but this is true of some of the other types of treatment as well, and in 1947 Walker kindly informed me that he and others have repeatedly used this therapy successfully in the years intervening since his report. Dickie (1946) reported astonishingly good results in ten cases from the intramuscular injection of liver extract as in the treatment of pernicious anemia. Thiamine, favorably reported upon some years ago, has fallen by the wayside. I have recently heard of benadryl and pyribenzamine being used successfully; one wonders what will come of this

PRURITUS ANI

There are many ascertainable causes for itching about the anal region, such as constipation, colitis, cirrhosis, carcinoma, anal fissure, hemorrhoids, pinworm infestation, bacterial or mycotic infections, diabetes mellitus, allergy, psychogenic mechanisms, mechanical factors, etc. Removal of the cause will bring complete relief in many instances, but there also exists a class of cases to which the word "idiopathic" can be correctly applied since they are associated with no demonstrable etiologic factors and respond but poorly to the milder types of treatment. Very interestingly, however, Foster and Hill (1940) have drawn attention to the frequency with which attacks of pruritus ani occur in association with exacerbations of seborrheic dermatitis of the scalp, ear canals, eyelids, umbilicus, or axillas, or of dermatophytosis of the feet.

Psychotherapy.—Swinton (1947) stressed the importance of pointing out to patients the value of rest, relaxation and freedom from nervous tension, and that if the patient is given a brief intelligent discussion of the subject he may often be led to suggest etiologic factors that obviate expensive study and consultation.

Local Hygiene.—It is well-known that the elimination of toilet paper and washing instead with cotton moistened in warm water will alone control many mild cases; this is particularly true if the use of soap in the anal region is avoided.

are performing perianal subcutaneous neurotomy which they say is effective in stopping the itching Cantor (1943) in some instances combined the tattoo and neurotomy approaches. Swinton (1947) said that he had had no experience with this undercutting type of operation Rugeley's (1946) experience suggested the advisability of thoroughly investigating the possibility of allergic sensitization in cases of pruritus ani before resorting to radical procedures

X-Ray.—This agent, in the hands of a properly qualified expert, will by no means relieve every case but it does have some brilliant successes to its credit. However, Swinton (1947) said that in his experience itching recurs in practically all cases after six to eight months of temporary relief and that the cases are invariably then much more difficult to control; he said also that he had observed cases in which cancer had developed from the excessive use of radiation therapy in the anal region

Aminophylline and Papaverine.—Epstein (1946) described the intravenous administration of aminophylline as in asthma (*q v.*) with satisfactory results in a series of cases of pruritus, none of these were pruritus ani, still the response was good and it might be worth trying the drug in the malady under present consideration He found aminophylline ineffective as an antipruritic agent when administered orally, rectally or locally. Wirth (1947) described the satisfactory intravenous administration of papaverine hydrochloride in a group of patients suffering from skin eruptions of various types; there were no cases of pruritus ani, but again the agent might be worth trying in intractable cases of the latter malady Wirth injected 1 grain (60 mg.) slowly intravenously.

Narcosis.—MacCormac *et al.* (1946) described the employment of continuous narcosis—a specialist type of therapy—in a group of cases including a few of pruritus ani, they seemed to feel that sufficient improvement was had to justify the therapy, but it is difficult for the objective reader of their report to find evidences of very marked effects.

SCABIES

Scabies is an infectious disease caused by an animal parasite, *Sarcoptes scabiei*, the female of which incites the itching by burrowing into the skin in order to lay her eggs. These burrows, which are tortuous and marked by a slight elevation at one end and a grayish speck at the other, can be seen with a strong hand lens. The sites of predilection are the dorsal surfaces of the webs between the fingers, the anterior axillary fold, the lower abdomen, the nipple region in the female and the shaft of the penis in the male. In cleanly individuals the spread is usually not beyond these points, but in dirty individuals and in severe cases the whole body may be involved, though the face and scalp nearly always escape. In children the palms and soles are also often infested, superimposed eczematous and impetiginous lesions are also frequent in young patients and in patients of any age who do not resist the desire to scratch excessively The disease probably never disappears spon-

"The perianal skin is cleansed with tincture of green soap and painted with Scott's solution (mercurochrome crystals 2 parts, distilled water 35 parts, acetone 10 parts and alcohol 55 parts) or tincture of merthiolate (1:1000). One ampule of *nupercaine-phenol-benzyl alcohol in oil*, which has been slightly warmed to facilitate the flow of oil, is drawn into a 5 cc. sterile glass syringe through a large caliber needle. The needle is then changed to one of gauge No. 21, 1¾ to 2 inches long The perianal region is then divided into four quadrants, and usually either the left or right posterior quadrant is chosen first The patient should lie in the Sims' position, on the side selected for the treatment The needle is inserted subcutaneously about one-half inch outside the affected area. *It must be freely movable at all times* The solution is then injected in fan-shape manner until all the 5 cc. have been used. *The injected tissues are massaged gently for about 3 minutes* with a sterile piece of gauze, thus assuring an even distribution of the oily solution. The second injection is given 2 days later in the opposite posterior quadrant, and, at 2-day intervals, [illegible]

cause if more than one quadrant of the muscle has been injected, the anal canal may become patulous and temporary loss of control take place."

Dye Therapy.—Allen (1947) said that he had found the dye therapy developed by Berwick a good many years ago often very beneficial, the agent acting in his opinion not only as a bactericide but also as a fungicide. Berwick's dye consists of a mixture of 1 per cent brilliant green and 1 per cent crystal violet in 50 per cent alcohol. Allen used the dye treatment twice weekly in the following manner: if the patient is suffering much pain, anesthetic in oil is injected subcutaneously and 5 per cent phenol is applied to the erosions. The dye is then applied thoroughly and is followed by the application of tincture of benzoin compound After the alcohol in the benzoin compound has been evaporated by a fan, a bland powder is applied to the area and a gauze dressing attached to protect the clothing overnight. The patient is allowed to take a bath the next morning but instructed to use no soap in this area The office treatment is further aided by the prescription of a fungicidal ointment or powder, Allen used "Desenex" ointment, composed of undecylenic acid and zinc salts, or a mixture of these ingredients in powder form.

Tattooing.—Just about the most bizarre of the thousand and one treatments advocated for control of pruritus ani is the tattooing of the region with mercury sulfide. Turell (1940), and Cantor (1943), reported good results in cases refractory to other more usual types of treatment, but it would seem that this is a specialist's type of therapy Allen (1947) said that his experience with tattooing had not been satisfactory although he had used it in a fair number of cases.

Surgery.—Swinton (1947) said that while there are definite indications for surgery in some of these patients, as his experience has increased surgery has been used less and less. He said it should be directed toward removal of sources of infection and the correction of obvious local disease. Infected crypts should be drained, anal fissures should be excised and fistulas removed, a contracted anal canal should be corrected, enlarged edematous skin tabs that interfere with local hygiene of the area should be removed. He said that the routine removal of hemorrhoids relieves few patients. Some surgeons

in an emulsion with benzyl benzoate and found that the use of this formula had practically no advantage over the usual benzyl benzoate emulsion and that furthermore the use of DDT alone was ineffective.

Tetmosol.—This agent is tetraethylthiuram monosulfide, conveniently shortened to "tetmosol." So far as I am aware the studies have been confined to England and have been of a rather experimental nature. Clayton (1943) employed a formula containing tetmosol 25 per cent, polyglycerol ricinoleate 10 per cent, alcohol 65 per cent. He made three or four applications of this mixture at three- to four-day intervals and was very pleased with his results in a small series of cases; dermatitis was not induced. Bradshaw (1944) found a lotion containing 6.25 per cent of tetmosol reliably effected cure in three days in 97 per cent of sixty-seven cases; the patient was given a hot scrub bath, dried and the lotion applied and then the clothing put on after allowing time for the lotion to dry, the seance being repeated on three successive days. Bartley *et al.* (1945) substituted 5 per cent tetmosol soap for ordinary soap in a closed community of 400 persons with the following results: during eighteen weeks when an ordinary soap was used, twenty-one new cases of scabies occurred, during the thirteen weeks after the substitution of the tetmosol soap only one new case occurred and that during the first six weeks; no instances of dermatitis were recorded. Mellanby (1945) also found this a most excellent method not only of preventing but of curing scabies.

Sulfur.—*The older method* of using sulfur to combat scabies was advocated by Pillsbury *et al.* (1942) in the Military Manual of Dermatology. After a vigorous soap and scrub bath, sulfur ointment of 10 to 15 per cent strength (U.S.P XIII sulfur ointment is 15 per cent) is rubbed in vigorously with special attention to the regions of predilection, a thick coating of ointment being left on and the patient put to bed wearing clean pyjamas. This treatment [illegible]

necessary after drying the body, and retires in clean pyjamas in a clean bed. Carpenter *et al.* (1946) said of the employment of this method in the Navy that it produced a rather high incidence of secondary dermatitis necessitating a few days of soothing therapy before the patient could be returned to duty and that the treatment was not popular with the patients who not only resented their slimy existence but were forced to remain in pyjamas. In ordinary civilian practice it is customary to apply the ointment only at night, the treatment period being extended through five nights in some instances.

The "Danish" method of using sulfur is thought by many to be superior, but the opinion is not unanimous, quicker it certainly is, but some men claim it is less effective than the slower method and more likely to be followed by dermatitis. The patient merely applies the ointment—which is a rather complex one and now available commercially as Tilden's Danish scabies ointment and also as Scabicide of the Upjohn Company—after a preliminary bath and drying, goes to bed for twenty-four hours, and then removes the ointment, with bath and clean linens as in the older method.

SCHISTOSOME DERMATITIS

(*Swimmer's Itch*)

(See chapter on Flukes)

(1944) figures showed that irrespective of the size of the family, if scabies gains an entrance to the houschold 80 per cent of the members are infected. As long ago as 1687, Bonomo showed that scabies is associated with the presence of *S. scabiei;* indeed this was the first infectious disease to have its etiology established.

THERAPY

Benzyl Benzoate.—Kissmeyer popularized the use of this agent in 1937, and the British epidemic during War II fully established its superiority to sulfur; the study of Mellanby *et al* (1942), in which benzyl benzoate was compared with many other agents, was the most exhaustive. The impression of many observers, confirmed by the studies of Lunn (1942), is that benzyl benzoate is just as effective whether a bath is given beforehand or not, though in very severe infections in which there is incrustation it is still considered advisable to give a good scrubbing bath before applying treatment. Experience has also shown that one thorough treatment may be all that is needed; the definitive experiment in this connection was that of Mellanby (1944), who reported an incidence of 26 per cent of scabies among the female patients in a large institution for the insane—after a single treatment of all 804 patients (without preliminary baths), and of such members of the staff as were infected, all evidence of the disease disappeared and there was only a negligible number of recurrences. However, most men still use the agent twice on successive days. Kissmeyer's original formula consisted in equal parts of benzyl benzoate, isopropyl alcohol and soft soap, but during War II several complex lotions and creams were devised that were allegedly less irritant. However, as these preparations contained ingredients not widely available, it is still customary in civilian practice to employ the Kissmeyer formula. Carpenter *et al.* (1946), using two applications daily for two successive days, followed by a hot soapy shower, found that on the whole therapy with this benzyl benzoate emulsion was well tolerated and accepted despite the sensation of burning and smarting in the skin that occurred with each application and the superficial exfoliation of the scrotum resulting from repeated treatments. It seems that benzyl benzoate may also be effectively used merely in simple 33 per cent solution in isopropyl alcohol. Humphrey (1946) said he had found that the simplest way to treat scabies in men returning from abroad was to paint the body from the neck down with this solution for two successive days.

Benzyl Benzoate and DDT.—A reputedly highly effective technic employed in the Army (Bulletin U.S. Army Medical Dept., 5, 128, 1946), consisted in having the patient shower and scrub himself thoroughly and then be sprayed from chin to toes with the following mixture:

	Per Cent
Benzyl benzoate	10
DDT	1
Procaine hydrochloride	2
Ethyl alcohol to make the desired quantity.	

The patient put on clean clothing and was instructed not to bathe until the next day, when upon returning he was again sprayed and instructed not to bathe for at least twenty-four hours. It was said that more than 97 per cent of the individuals so treated were completely relieved of all symptoms and that there was no complaint of more than a temporary local burning in all the 1266 patients treated. However, Franks and Dobes (1946) used DDT

ACUTE POISONING

THE CORROSIVE ACIDS AND ALKALIS

The corrosive acids and alkalis most frequently swallowed accidentally or with suicidal intent are sulfuric, nitric, hydrochloric and oxalic acids, sodium or potassium hydroxide (lye), sodium or potassium carbonate, and ammonium hydroxide (household ammonia). The general symptoms of the group are: [illegible]

and other products; profuse bowel movements that are at first normal but later contain blood and shreds of mucosa, respiratory symptoms due to contact of some of the corrosive material with the air passages, and quick shock and collapse Those escaping immediate death may succumb to perforation [illegible]

deprivation symptoms, such as cramps, headache, convulsions, etc.

THERAPY

Acids [illegible]
serve, it should be g[illegible]
Later, milk, egg w[illegible]
substance such as
drugs as indicated The value of morphine or dilaudid in decreasing pain and thus perhaps avoiding shock should not be overlooked Keep the patient warm

[illegible]

too small a dose of the oxal[illegible]

[illegible]

ntidotes, usually in
with water Crowe
patients with early

lice in about half an hour, and that therefore latterly he had been having the hair washed one hour after treatment and the usual combing carried out then; in so far as could be judged from the small series, this speedy method appeared to be as successful as the longer one. In the cases in Frazer's series in which the scalp was secondarily infected, the lice were attacked first and then on the second day when no live lice were present the hair was cut as required and the septic area attended to.

Other Agents.—With DDT so highly effective and now universally available, I do not feel justified in devoting space to a consideration of any other agent; the especially interested reader is referred to the Fifth Edition of this book.

CRAB LOUSE INFESTATION

DDT.—In a concentration of 10 per cent in talcum or pyrophyllite, DDT is used with high effectiveness against pubic lice. The powder is applied to all the hairy portions of the body and rubbed in thoroughly and allowed to remain on for twenty-four to forty-eight hours before bathing; the treatment is to be repeated seven to ten days later. Sutton (1945) reported the satisfactory employment of 0.5 per cent DDT in cold cream, one-half ounce (15 gm.) of this ointment being rubbed into all the hairy portions of the body (it should be noted that in hairy individuals this practically amounts to anointing the whole body with the preparation), waiting twelve hours, and then taking a bath with soap and water. He said that with the use of this preparation itching stops within thirty minutes, that the pediculi are dead at this time, that the nits do not hatch, and that irritation does not occur.

Other Agents.—See statement following this heading in the article on Head Louse Infestation above.

MITE INFESTATION

During War II it was shown that the most important individual protective measure for the prevention of scrub typhus is the impregnation of clothing with chemicals that kill the mite before it becomes attached to the skin. In our Army originally a 5 per cent solution of dimethylphthalate and 2 per cent soap was employed, the clothes being immersed in this solution and then wrung out and hung up to dry, being ready to wear when dry. Later an emulsifying agent was added so that the soap was omitted. However, Fairley (1946) said that the large-scale employment of dibutyl phthalate in the Australian forces proved exceedingly efficacious, McCulloch (1946) having shown that this preparation is better retained in clothing than dimethyl phthalate. Toward the close of the War we therefore shifted to dibutyl phthalate as rapidly as a supply became available to us, and then 5 per cent benzyl benzoate was substituted to some extent for the dibutyl phthalate. It is said that thorough treatment of clothing with either benzyl benzoate or dibutyl phthalate withstands wading through streams and at least two launderings with soap and hot water. However, in contrast to dimethyl phthalate, neither dibutyl phthalate nor benzyl benzoate repels mosquitoes

and peanut oil) were injected intramuscularly. One to two hours after this initial dose the patient was given a 150 mg. dose, which was usually followed in four to six hours by another dose of 150 mg. In several patients still a third dose of 150 mg. was injected before twelve hours had elapsed. Of the series, three patients received 450 mg. of BAL in twelve hours; twelve patients received 600 mg.; one patient 620 mg.; and five patients 750 mg. During the second twelve hours the patients received one or often two injections of BAL; thereafter two doses of 150 mg a day were given as a rule for one to two days more, depending somewhat on the general condition of the patient. [illegible]

an occasional patient complained of abdominal pain within twenty minutes after the first injection. In many patients a rise in blood pressure was recorded during the first twenty-four to forty-eight hours, but it was felt doubtful that, in the absence of other symptoms, this change could be ascribed to the injections of BAL. However, subsequent experience in three additional patients indicated that perhaps the dosage employed in this study may be about at the upper range of safety

The patients fell into three groups: eight of them swallowed not more than 0 5 gm. of mercuric bichloride and treatment with BAL was started from twenty minutes to three and one-half hours later, all made a prompt recovery. Six patients swallowed 1 gram and five were treated within one to three and [illegible]

gm. Eight of these patients were treated with BAL from one and a quarter to three and a half hours after taking the agent and one patient was treated nineteen hours after having swallowed at least one and a half grams; the latter patient was entirely well in three weeks and the other eight patients recovered completely in two and a half to seven days

In summarizing this remarkable report, Longcope *et al* said that BAL should be given in an initial intramuscular injection of 300 mg followed within the first twelve hours by two or even three further injections of 150 mg each The mortality rate in this group of cases, combined with that in the [illegible]

nineteen additional patients were treated bringing the total in the series to forty-two. The results emphasized the great importance of instituting this form of therapy within the first few hours after the patient has swallowed the agent, recovery occurred in all thirty-seven patients, irrespective of the size of dose and intensity of symptoms, treated with BAL within four hours of swallowing the poison. Another comparison was made as follows: taking an analogous group of cases admitted to the hospital before the use of BAL and eliminating the patients in that group and in the BAL treated group who took only 0 5 gm of mercuric bichloride (recovery occurred in all of these cases in both groups) there were eighty-six patients in the control group admitted within four hours after swallowing bichloride and twenty-

[illegible]

PHENOL (CARBOLIC ACID) AND LYSOL POISONING

The symptoms are those of corrosive poisoning with additional early evidences of severe nephritis. The toxic action on the cardiovascular and central nervous system is pronounced and almost immediately manifested; death sometimes occurs in a few minutes, often within the hour.

THERAPY

Lavage, supportive treatment, morphine or dilaudid, and the later use of [illegible]

able; it should be used by lavage, 4 drachms (15 gm.) to the pint (500 cc.) of water, the washing to be continued until the phenol odor disappears The chemical rationale of the employment of this agent has come to be doubted in recent years, but the measure is a very valuable one nevertheless, perhaps due to some hindrance it offers to absorption plus the induced purgation.

Alcohol has been shown by clinical and experimental observation to be of no value. The same is true of glycerin. Indeed, alcohol if given as an antidote after the poison has been taken may hasten death, despite the well-known fact that a drunken individual swallowing phenol is not so seriously affected *as is a normal person. These apparently contradictory facts are not understood.*

MERCURIC CHLORIDE (BICHLORIDE) POISONING

By the time the patient is seen he has usually vomited so profusely that he is now merely retching unproductively or at most is bringing up pink mucoid material, often he is passing reddish watery stools Abdominal pain is usually very severe unless the patient is already in shock.

THERAPY

Emergency treatment consists in lavaging the stomach and leaving in it a pint of milk or several raw eggs, the whole egg being just as valuable in precipitating bichloride as egg white. Sodium formaldehyde sulfoxylate in 5 per cent solution is more valuable than water alone for washing out this stomach for it reduces mercuric chloride to mercurous compounds. As quickly as possible the administration of BAL must be begun.

BAL.—Longcope *et al.* (1946) presented the observations made on twenty-three patients treated at Johns Hopkins Hospital with BAL after having swallowed from 0.5 gm. to 20 gm. of mercuric chloride. On admission the patients were lavaged with 5 to 10 per cent sodium formaldehyde sulfoxylate, and 300 mg of BAL (*i.e.*, 3 cc. of a 10 per cent solution in benzyl benzoate

less today they would add penicillin) in the attempt to prevent pneumonia and desirable, where conditions permit, to protect the liver with a diet containing generous amounts of carbohydrate and protein and little fat, together with liberal use of vitamin supplements.

In one of the two cases of gasoline poisoning in adults, due solely to inhalation of the fumes, reported by Lawrence (1945), violence became so great after recovery of spontaneous breathing that intravenous barbiturates had to be given in order to effect control

TURPENTINE POISONING

Turpentine poisoning appears rarely in the literature. Ross and Brown (1935) recorded seven cases with one death in a statistical study of poisonings in children at the Toronto Hospital for Sick Children, but they did not describe the cases save to list the death as due to aspiration pneumonia. Harbeson (1936) wrote: "Some people exhibit a decided idiosyncrasy toward turpentine. In these, 30 minims will cause vomiting and diarrhea. In larger doses there is an acute enteritis, vomiting of mucus, which is often bloody, diarrhea and passage of blood-stained mucus. Large doses have a marked effect on the kidneys, causing albuminuria, hematuria, and even complete suppression." His own patient, an infant of eleven months, died in shock a few hours after the administration of 2 teaspoonfuls of spirits of turpentine by the grandmother who "thought the child had worms"—it is really a wonder that any of us are alive.

ACUTE ARSENIC POISONING

Acute arsenic poisoning is not rare, due to the fact that the arsenical pigments are much used in the arts and industries, rat and some fly and roach [illegible]

[illegible]

colicky pains are very severe and the patient often goes into shock. The stools are of the rice-water type and conceivably might cause some difficulty in differentiating this condition from Asiatic cholera. There is immense thirst, scanty and albuminous urine, and finally suppression of the urine. If death does not come in a few hours to a few days, paralyses of the lower extremities are frequent, as is also fatty degeneration of the liver and kidneys.

THERAPY

[illegible]

seven of these died; there were twenty-five patients in the BAL-treat group admitted under similar circumstances and none of them died.

The toxicity of BAL is discussed fully in Syphilis.

Other Measures.—Of course in patients seen too late to be effectivel handled with BAL, shock, dehydration and salt depletion are to be com bated by the usual methods. As for surgical measures in anuric patient Abeshouse (1945) felt that decapsulation is contraindicated unless oliguri and anuria have developed in spite of a trial of cecostomy.

GASOLINE AND KEROSENE POISONING

The most comprehensive report of gasoline and kerosene poisoning to dat is that of Nunn and Martin (1934), who summarized the findings in seventy two cases in children. Total mortality was 11 per cent, the children who finally succumbed having lived from two to eighteen hours after ingestion ingestion alone need not cause ness, incoordination, cyanosis, gns of pulmonary involvement, which lasted only a few hours, the children were apparently out of danger. But in the patients who aspirated as well as ingested one of these petroleum products the picture was much graver owing to the rapid development of pneumonitis, as evidenced by cough and many moist râles throughout both lungs. These patients developed rapid and weak respiration and pulse, became cyanosed and restless, and developed coma and convulsions, and often died. However, Lavenstein's (1945) patient developed pneumonia, pneumothorax, pneumopericardium and subcutaneous emphysema after ingesting kerosene, and survived. In the thirty-three patients of Lesser *et al.* (1943), pulmonary manifestations were observed in 77 per cent of those examined roentgenologically as compared with only 24.2 per cent found by physical findings alone. Waring (1933) found no evidences of methemoglobin formation in the blood.

THERAPY

Patients who have only ingested the poison seem to respond well to emptying of the stomach, stimulation and catharsis Machle (1941) stressed the importance of lavage even though forty-eight hours or more have elapsed before treatment is begun, and Deichmann *et al.* (1944) thought it highly important to continue it until the odor of kerosene is no longer detected in the washings; but Lesser *et al.* (1943) felt that, since lavage may provoke aspiration, it is probably inadvisable to employ it unless the amount of kerosene ingested is very large.

No really effective treatment has been developed for patients who have also aspirated the poison. Nunn and Martin felt that oxygen-carbon dioxide therapy was helpful in their later cases; however, Deichmann *et al.* (1944) pointed out that kerosene remains in the lungs because of its low volatility and that increased pulmonary ventilation would likely have no beneficial effect other than to prevent anoxia or to eliminate it if already present. These last observers also felt that kerosene reaches the lungs not only by aspiration but by way of the blood stream after absorption in the gastrointestinal tract; and they felt it permissible to employ sulfonamides (doubt-

cent solution of sodium thiosulfate (b) Stop administration of the amyl nitrite and inject 10 cc. of the sodium nitrite solution at the rate of 2.5 to 5 cc. per minute. (c) Inject by the same needle and vein, or by a larger needle in a new vein, 50 cc. of the sodium thiosulfate solution. The injection of both agents may be repeated in half-doses if signs of poisoning reappear.

Methylene Blue.—Hanzlik (1947) said he had no doubt of the high level of efficiency of the nitrite-thiosulfate combination in the hands of expert physicians who have experience with the technic, but that he felt, and he thought it was the feeling of the staffs of the emergency hospitals in San Francisco, that the practitioner who rarely treats a case of cyanide poisoning would do well to try the methylene blue treatment first because it is devoid of the objectionable circulatory depression that may occur during the nitrite-thiosulfate treatment. The technic of employment of the methylene blue treatment in the emergency hospitals of San Francisco, as it was described by Hanzlik and Richardson some years ago, is still, according to a recent communication from Hanzlik, employed. It is as follows: "Inject immediately 50 cc. of a 1 per cent solution of methylene blue (containing 1.8 per cent of sodium sulfate) intravenously; repeat, if necessary, until a total of 200 cc. is injected. Frequently, consciousness and reflexes are restored before the first 50 cc. is completely injected, but if the patient lapses into unconsciousness, or manifests respiratory depression, resume the methylene blue treatment. As quickly as possible, proceed with gastric lavage, using 5 per cent sodium thiosulfate, this oxidizes any unabsorbed poison."

STRYCHNINE POISONING

The presence of strychnine in some of the vermin exterminators has led to instances of accidental acute poisoning in rural regions, but most of the recorded cases, except in children, have been suicidal or homicidal, for the dangerous nature of the drug is so well known as almost to preclude its careless handling. The patients usually say that there is a peculiar feeling at the beginning of each paroxysm, like a slow electric shock that starts above and behind the eyes and sweeps over the whole body, then the spasm begins. The usual position is that of opisthotonos. The spasms last from one-half to five minutes with complete relaxation between. Consciousness is not lost and the suffering is excruciating. Between spasms there is a sensation of approaching death and the patient will plead for someone to hold him, seeming to feel that he is being ruthlessly hurled into oblivion. The usual interval between spasms is five minutes or more, most patients not surviving more

sounds, absence of opisthotonos, unconsciousness, or mania, *eclampsia*, complete unconsciousness during and between spasms, absence of complete opisthotonos

the poison perhaps pocketed in the upper part of the gastro-intestinal tract. If no stomach tube is available when the patient is first seen, or if its introduction is impossible or considered to be inadvisable, the emetic drugs should be resorted to, for this stomach must be thoroughly emptied:

Household mustard	1 to 2 drachms (4-8 gm.) in water
Ipecac	1 drachm (4 gm.) of the powder or 4 drachms (15 cc.) of the syrup, in water
Copper sulfate	7½ grains (0 5 gm.) in water.
Zinc sulfate	30 grains (2 gm) in water.
Apomorphine hydrochloride	1/10 grain (6 mg) hypodermically for a robust adult, 1/60 grain (1 mg.) for an infant.

The mustard is the least dangerous but also the least effective. The ipecac is uncertain in action and quite depressing. Both copper and zinc sulfates cause vomiting in a very few minutes, and under the conditions obtaining here, *i e.*, where there are no corrosions of the gastric mucosa, they are not rapidly absorbed and hence are usually not very depressing. However, if they do not cause emesis, further attempt should be made to get them out of the stomach for the reason that they are very irritant; they are little employed nowadays. Apomorphine is a reliable emetic but it is well known that the after-depression is sometimes great.

BAL.—This agent is being very effectively used in the treatment of acute arsenic poisoning. For methods, see Mercuric Chloride Poisoning; the toxicity of BAL itself is discussed fully in Syphilis.

CYANIDE POISONING

These patients are practically always in coma when the physician reaches them. There may be muscular spasms with perhaps even moderate opisthotonos. Respiration is by this time usually very shallow and irregular and the pulse of a very poor quality if perceptible at all; cyanosis is usually marked, the pupils often widely dilated. In many cases the urinary sphincters are relaxed, there may also be froth at the mouth and the odor of cyanide on the breath Such patients may surprisingly remain alive an hour or more after presenting this picture.

THERAPY

Artificial respiration and oxygen inhalation, gastric lavage with sodium bicarbonate solution, and the usual stimulants are tried in most cases and practically always without results. In recent times, however, the nitrite-thiosulfate treatment, which seems to be favored by the National Safety Council, has come to the forefront of attention; the somewhat newer employment of methylene blue will also be described below.

Nitrite-thiosulfate Therapy.—In this treatment a *nitrite* is administered systemically to the patient and this is followed immediately by the systemic administration of sodium thiosulfate; the rationale of this therapy probably lies in the conversion of hemoglobin into methemoglobin by the nitrite, the coupling of the cyanide ions to the methemoglobin to form cyanmethemoglobin, which has a relatively low toxicity, and the stimulation on the part of the sodium thiosulfate of the rhodanase conversion of cyanide to thiocyanate. Chen *et al* (1944), who reviewed fifteen cases treated by this combination of nitrite-thiosulfate therapy, fourteen of whom completely recovered,

chloral, the barbiturates (the first taken excessively in a drinking bout, the other three with suicidal intent usually), and carbon monoxide (inhaled accidentally or purposely in a closed room or garage)—this is the list.

Alcohol.—We are concerned here only with the final anesthetic stages of exceptionally severe acute alcoholism, since the hilarious and stuporous stages of an ordinary intoxication rarely come under observation for treatment as poisoning. The patient is in as deep coma as though chloral had been taken; the pupils are normal or dilated, never contracted. The skin is cold, clammy and pale, the respirations are somewhat slow and stertorous, the pulse is rapid and becomes increasingly weak, reflexes are lost and the temperature is considerably below normal.

Morphine.—The patient progresses gradually from an overpowering sleepiness into a deep coma from which it becomes finally impossible to waken him The respirations become slower and slower and finally irregular and stertorous, and then they stop, usually the heart has been relatively little affected and continues to beat for some time after respiration has ceased. In the beginning the skin is warm and moist, but later becomes cold, clammy and cyanotic; the pupils are constricted to the so-called "pinpoint" dimension, but they undergo a terminal dilatation. As death approaches the sphincters relax. Convulsions are rare in adults but are sometimes seen in infants.

Chloral Hydrate.—There is deep narcosis with constricted pupils, complete muscular relaxation, very slow and shallow respiration, barely perceptible pulse, cold clammy skin, rapid fall of temperature and blood pressure.

Barbiturates.—In a severely poisoned patient the symptoms are deep narcosis with constricted pupils, slow and shallow respiration (or perhaps rapid and jerky, depending upon the depth of the depression), rapid feeble pulse, cyanosis, pronounced fall in blood pressure and temperature, depressed or absent reflexes. The increasing importance of barbiturate intoxication as a problem confronting the medical profession has been emphasized in recent years by numerous writers, perhaps most notably Burdick and Rovenstine (1945), who said that in New York City alone barbiturate suicides approximately doubled in the five-year period 1937 to 1941. However, Kempf (1946) said it had been their observation over a period of years at the Indianapolis City Hospital that when barbiturates are taken with suicidal intent death rarely ensues unless doses of 100 to 150 grains (6.5 to 9.7 gm.) of barbital or phenobarbital are ingested, that with amytal 90 grains (5.8 gm.) or more do not cause death except in patients with other complications; and that even with seconal and pentobarbital (nembutal), adult patients ingesting less than 50 grains (3.25 gm.) do not die when given proper treatment.

Carbon Monoxide.—The patient is comatose and has a peaceful expression, though there is often twitching of the facial muscles; the temperature is usually

ticularly on the arms The early symptoms are entirely due to the fact that

other variable factors), the prognosis for recovery is good, but if profound

THERAPY

Initiated clinically by Zerfas and McCallum, in 1929, and subsequently substantiated both experimentally and clinically by numerous observers, the barbiturate treatment of strychnine poisoning has almost completely obliterated the horror with which physicians were formerly wont to view these terrible cases. Below is a condensed version of the barbiturate method, presented by Kempf, McCallum and Zerfas (1933) in reporting eleven cases successfully treated

(1) Give just enough sodium amytal or sodium pentobarbital (nembutal) solution intravenously to put the patient to sleep, or, if in convulsions, to stop them If using phenobarbital sodium, aim just to stop the convulsions, even though sleep is not induced.

(2) Return of heightened reflexes, complaints about noises, marked response to slight stimuli, or convulsions, call for repetition of the antidote.

(3) Gastric lavage is unnecessary and inadvisable and should be done in no case unless the patient is asleep and there is adequate assistance to prevent injury or aspiration of material from the stomach. Apomorphine should not be given as it increases the latter tendency

(4) Morphine is not indicated, but quiet dark surroundings are recommended and ether may be used to control convulsions until a soluble barbiturate can be given.

(5) One should distinguish carefully between strychnine action and barbiturate effects before giving second or third barbiturate injections; if in doubt wait for a mild convulsion.

(6) If barbiturates suitable for intravenous injection are not available, give any barbiturate by mouth in dosage not to exceed the equivalent of 15 grains (1 gm) of sodium amytal for the adult; *i.e*, in an amount not to exceed five times the ordinary hypnotic dose, as stated under Insomnia.

POISONS CAUSING STUPOR OR COMA

The types of unconsciousness likely to be encountered in a private general practice, or in the receiving ward of any busy metropolitan hospital, are such as occur in the following states: (1) shock following trauma, burns, hemorrhage; (2) electric shock; (3) sunstroke, (4) eclampsia; (5) diabetes mellitus; [illegible] (10) central

[illegible] emis

[illegible] aria

(rare outside the malarial zone, of course); (14) meningeal form of acute

[illegible]

[illegible] and maintain it so firmly that

[illegible] ipal things to com-

[illegible] ne or other opiates,

fifteen to thirty minutes as indicated; and should regression develop, the same dose is given intravenously until the desired plane of activity is re-established. These observers said they had gained the impression that the initial response to picrotoxin following depression from an overdose of the longer acting barbiturates, such as barbital or phenobarbital, is slower than is the case with the shorter acting ones, and that therefore the drug should be given in smaller amounts in barbital and phenobarbital cases if its accumulation with the resultant sudden and severe stimulation is to be avoided. In a patient who was unconscious for four and a half days following the taking of a large amount of barbiturate, Misr (1946) recorded the administration of 1745 mg. of picrotoxin, the 5 mg. injections being given at fifteen-minute intervals intramuscularly except the first, which was given intravenously. [illegible]

Regarding the use of analeptics in carbon monoxide poisoning, Henderson trenchantly remarked "The less the ambulance surgeon uses his hypodermic syringe on patients with carbon monoxide asphyxia, the better."

Oxygen-Carbon Dioxide.—In carbon monoxide poisoning the patient is likely to be breathing very poorly when found. Artificial respiration must be started at once and continued until the breathing becomes spontaneous. Henderson and Haggard conclusively showed the value of the inhalation of oxygen plus carbon dioxide In the beginning, 5 per cent of the latter was advocated, later 7 per cent, which I believe is still looked upon by most men as the ideal concentration, though 10 per cent is advocated by some men of experience. Continuance of this gas treatment beyond one and one-half hours is useless, since by that time practically all the carbon monoxide will have been eliminated

The value of administering oxygen-carbon dioxide in acute alcohol and barbiturate poisoning cases seems to be questionable, though Burdick and Rovenstine (1945) felt the measure justified in severely depressed cases of the latter type.

Intravenous Fluids.—The parenteral introduction of fluid to insure proper hydration and nourishment and enhance renal function seems a rational procedure, which of course should be adjusted to the individual patient's need; Burdick and Rovenstine (1945) felt that in barbiturate cases 2 liters of 5 per cent glucose in normal saline, and 1 liter of 5 per cent glucose in water, given slowly meet the twenty-four hour requirements of the average patient. Of course in some instances consideration will have to be given to the administration of amino acids intravenously, and perhaps in all cases if the patient remains unconscious for more than twenty-four hours vitamin B should be [illegible]

asphyxia has persisted for very long, recovery *does not take place even after* all of the carbon monoxide has been released and eliminated; in these cases there has been irremediable brain injury. Many of the late deaths are also due to pneumonia.

THERAPY

Maintenance of Airway.—It is of major importance in all the types of stuporous poisoning to establish quickly a patent airway and to see that it is *maintained throughout the period of treatment.*

Gastric Lavage.—Alcohol, chloral, or the barbiturates being taken by mouth, it is rational to empty the stomach thoroughly; lavage with warm water is the measure of choice because it accomplishes washing as well as emptying, also for the reason that emetic drugs are very ineffective in these depressed states. If morphine was swallowed lavage is equally indicated, but careful animal study has shown that when this drug has been injected subcutaneously (as is usual in suicide cases) the small amount excreted into the stomach is very doubtfully of any importance in the final outcome; lavage is in great clinical favor, however, even in these instances, one good reason being, as pointed out by Burdick and Rovenstine (1945), that the possibility [illegible] is a real danger in a coma- [illegible] tube [illegible] ed to the development of lung complications.

Stimulants (Analeptics).—A desperate effort is made to rouse the patient from stupor and to combat respiratory and circulatory depression by the use of "stimulants" injected in large doses subcutaneously or intramuscularly. As a matter of fact, it is very difficult exactly to assess the value of any of these agents for they are usually used in conjunction with other measures. The older drugs are: caffeine sodiobenzoate, $7\frac{1}{2}$ grains (0.5 gm.), or black coffee at body temperature by rectum; metrazol, $1\frac{1}{2}$ grains (0.1 gm.); coramine (nikethamide), 5 cc.; ephedrine, 5/6 grain (50 mg.); benzedrine (amphetamine), $\frac{1}{4}$ grain (15 mg.). The employment of heroic dosage of strychnine sulfate, 1/20 to 1/10 grain (3 to 6 mg.), or atropine sulfate, 1/40 grain (1.5 mg.), seems to me unwarranted upon the basis of either laboratory or clinical experience.

Picrotoxin was added to t [illegible] has proved its worth, partic [illegible] stine (1945) felt that either [illegible] its potency is responsible for the reluctance of many physicians to use it. They said in their opinion analeptic therapy should be conservative if the reflexes are active and motor activity present but vigorous *if the patient is* deeply depressed. In cases of the latter sort they felt it safe to continue administering the drug intravenously at the rate of 1/60 to 1/30 grain (1 to 2 mg.) per minute until the corneal, swallowing or other reflexes appeared, or until slight twitching of the facial muscles occurred; *beyond this point* convulsions may result, though these usually are of a mild nature and gradually subside as the stimulant is destroyed. Should such convulsions be severe or should milder ones continue, an intravenous barbiturate such as sodium pentothal may be given slowly *just to the point of control*. Once signs of reflex and motor activity have returned, picrotoxin shall be continued intramuscularly in maintenance dosages of 1/20 to 1/10 grain (3 to 6 mg.) each

IODINE POISONING

Accidental and suicidal poisoning with this substance is not rare It is usually swallowed in the form of the official tincture. There are severe gastrointestinal pain, vomiting, diarrhea, hemorrhagic nephritis, and depression and collapse.

THERAPY

Use the emetics (see Arsenic Poisoning) if necessary, but attempt to introduce the stomach tube as soon as possible and wash out with a starch decoc-

do not know to what extent this measure has ever been employed. At intervals introduce a demulcent to lessen the gastric irritation, such as eggs, milk, butter, liquid petrolatum. Of course the analeptic drugs (listed in Poisons Causing Stupor) may be used to combat the depression.

WOOD (METHYL) ALCOHOL POISONING

This type of poisoning, that increased so much in incidence in the United States during the first years following the introduction of so-called "prohibition," markedly declined as relatively safe contraband liquor became avail-

deliberately drink denatured alcohol. Unlike ethyl alcohol, which is oxidized readily, methyl alcohol is not fully oxidized in the body but is broken down into formic acid and formaldehyde, the result being acidosis of considerable degree If the intoxication is due to the ingestion of wood alcohol alone, symptoms may not appear for several hours, perhaps as long as a day or more, but if the methyl alcohol has only been a contaminant of ethyl alcohol the patient presents in a state of alcoholic inebriety from which he may partially recover before being seized by the characteristic symptoms of methyl alcohol poisoning; these latter are violent gastric pain and vomiting, disturbances of vision with dilated irresponsive pupils, dizziness, dyspnea, cyanosis, rapid weak pulse, and a period of delirium followed by collapse Individuals who survive are often totally blind.

THERAPY

For many years there existed some doubt of the contribution of the acidosis to the causation of the symptoms, but in the records of all the most recent outbreaks of wood alcohol poisoning—Kaplan and Levreault (1945), Jacobson *et al.* (1945), Province *et al* (1946), Chew *et al* (1946), and the monographic report of the exhaustive study of the subject by Røe (1946)—there has been

and kidney failure after receiving large doses of barbiturates for the treatment of his anxiety state. The patient was critically ill with cholemia and kidney failure at the time choline therapy was instituted, but from the data in the case it seemed justifiable to conclude that choline was a causal factor in the restoration of kidney and liver function, which started within twelve hours of its initiation; choline was given in daily dosage up to 120 grains (8 gm.) by intravenous drip, atropine being used in fairly large dosage to combat the severe sweating, bronchial secretion and painful abdominal cramps caused by the agent.

ATROPINE, STRAMONIUM AND HYOSCYAMUS POISONING

[illegible]

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THERAPY

In Comroe's (1933) case—a patient who had swallowed 7½ grains (0.5 gm) of atropine sulfate in solution one and one-half hours before being seen—gastric lavage with large quantities of sodium bicarbonate was performed in the receiving ward and 50 cc. of a saturated solution of magnesium sulfate was placed in the stomach. In the ward it was discovered that paradoxically the patient was suffering from acute pulmonary edema. After phlebotomy of 500 cc. an indwelling catheter was inserted and 400 cc. of urine obtained. When respiration became shallow, carbon dioxide and oxygen were administered. *A Jutte tube was passed and 5000 cc. of water given within forty-five* minutes, over half of which was vomited; continuous hypodermoclysis of saline solution was begun and cold sponges given in an attempt to reduce the fever. Maniacal outbursts were controlled with 2-grain (0.12 gm.) doses of phenobarbital. Morphine was not given because of the danger of deepening the late depression; pilocarpine was also withheld in the belief that myoneural junctions poisoned by atropine would not respond to it. The recovery of this patient, after the ingestion of 7½ grains of atropine, established a record until Alexander *et al.* (1946) reported their patient who recovered following the taking of double this amount; the recovery of this patient, which was com- [illegible]

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This type of poisoning, that increased so much in incidence in the United States during the first years following the introduction of so-called "prohibition," markedly declined as relatively safe contraband liquor became available and now in the postprohibition era is seen with relative rarity; though in our Armed Forces during War II several outbreaks of this type of poisoning occurred when men drank fruit juices to which some of this "alcohol" had been added usually in ignorance of the fact that it was a poison. In civilian life the victims currently are practically exclusively renegade vagrants who deliberately drink denatured alcohol. Unlike ethyl alcohol, which is oxidized readily, methyl alcohol is not fully oxidized in the body but is broken down into formic acid and formaldehyde, the result being acidosis of considerable degree. If the intoxication is due to the ingestion of wood alcohol alone, symptoms may not appear for several hours, perhaps as long as a day or more, but if the methyl alcohol has only been a contaminant of ethyl alcohol the patient presents in a state of alcoholic inebriety from which he may partially recover before being seized by the characteristic symptoms of methyl alcohol poisoning; these latter are violent gastric pain and vomiting, disturbances of vision with dilated irresponsive pupils, dizziness, dyspnea, cyanosis, rapid weak pulse, and a period of delirium followed by collapse. Individuals who survive are often totally blind.

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ATROPINE, STRAMONIUM AND HYOSCYAMUS POISONING

Rather mild degrees of poisoning with members of the belladonna group are frequently seen in practice; occasionally, also, serious poisoning occurs either in an individual with an idiosyncrasy for one of these drugs or in one to whom an overdose has been given. Where the various plants having this type of action grow wild, or are much used for ornamental purposes, children are now and then poisoned by eating the berries or seeds, or, as in one of Hughes and Clark's (1939) cases, through ingestion of brews of alleged anti-asthmatic properties made from them. The symptoms are very violent, but the prognosis as to life is good because of the rapid excretion of the poison. In fully developed cases the symptoms are exhibited in two phases: first, difficulty in swallowing, pain in the throat, great thirst, visual disturbances, nausea, redness of face and neck, rise in temperature, rapid pulse, and excitement that goes into delirium and often into mania; second, giddiness, staggering, stupor, respiratory and circulatory collapse.

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In the cases of Chew *et al.* response to treatment was usually prompt, as indicated both by clinical and laboratory criteria. Within a few hours dyspnea, nausea, cramps and mental symptoms abated and there was a progressive rise of plasma bicarbonate. Within twenty-four hours subjective blurring of vision had cleared in many of the cases, and at the time of discharge from the hospital in an average period of two weeks all but four patients had central vision as

[illegible]

therapy, and died in respiratory failure within three hours after admission.

ACETANILID, ANTIPYRINE AND PHENACETIN POISONING

Acute cases of poisoning with any one or a combination of these drugs are

[illegible]

the unique outbreak of this type of poisoning reported by Scott *et al* (1946), all the thirty-five newborn babies in a nursery developed relatively mild degrees of dye poisoning as a result of being swathed in diapers that were used without washing after being stamped with an ink containing an aniline dye. Other such instances have occurred, and in fact it seems that the first such outbreak was reported as long ago as 1886. Jones and Brieger (1947) reported a severe case of poisoning in a three-year old child who had eaten wax crayons containing an aniline dye

The symptoms of aniline poisoning appear somewhat suddenly and consist of depression and confusion, dyspnea, rapid weak pulse, methemoglobin cyanosis, clammy sweat, cold extremities and a subnormal temperature.

THERAPY

In the [illegible]
was perf [illegible]
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half hou [illegible]
hours af [illegible]
for at le [illegible]
number [illegible]
Carnrick *et al.* (1946) found this agent far more desirable for the purpose than methylene blue, which they felt might further increase the concentration of methemoglobin in the blood For the method of employing methylene blue see the article on Cyanide Poisoning Commenting upon their experience in the treatment of seventeen cases, Graubarth *et al.* (1945) said that neither methylene blue nor oxygen therapy is necessary and that the resort to transfusion is imperative only if the condition is acute and severe.

full recognition of the importance of combating acidosis as the primary requisite to success in treatment. In the outbreak recorded by Chew *et al.*, there were twenty-six patients who had ingested an estimated maximum of 540 cc of methyl alcohol and a minimum of 90 cc., the average amount being about 222 cc. Treatment was instituted in these cases from eleven to thirty-seven hours after the first ingestion of the poison, the average time interval being twenty-seven hours; the therapeutic results were excellent, and I shall therefore present their method in the following outlined form:

1. Draw blood for determination of plasma carbon dioxide-combining power which may be found to be as low as 10 volumes per cent.

2. Then administer alkali immediately as follows: (a) give intravenously 1 liter of 1/6 molar sodium lactate solution (Chew *et al.* advised that four 40-cc. ampules of molar sodium lactate solution be put into 1 liter of isotonic solution of 3 chlorides, but I have stated this in terms of the equivalent 1/6 molar sodium lactate solution since the latter is more likely to be available. If, however, sodium lactate solution is not immediately at hand, 5 per cent sodium bicarbonate freshly prepared—the water sterilized by boiling and then the sodium bicarbonate added after partial cooling—may be given in doses of 250 cc., this amount being equivalent to the liter of 1/6 molar sodium lactate solution. But the lactate solution is preferable for the reason that it yields the sodium ion more slowly into the system and thereby lessens the possibility of an uncompensated alkalosis.) (b) Give 1 drachm (4 gm) of sodium bicarbonate by mouth every fifteen minutes for four doses, or if the patient is comatose give it by stomach tube.

3. Repeat the above courses of lactate by vein and bicarbonate by mouth as shown to be necessary by frequent rechecking of the plasma bicarbonate. It was the experience of Chew *et al* that such courses had to be repeated three or four times consecutively in order to elevate the plasma carbon dioxide combining power to 40 or 50 volumes per cent. When this point is reached it may be checked twice daily until recovery is complete. If facilities are not available for the estimation of the carbon dioxide-combining power of the blood, the reaction of the urine may be used as a guide to the administration of the alkali. Chew *et al* used this reaction to regulate continued administration of sodium bicarbonate after the plasma bicarbonate had returned to nearly normal values, testing each voiding of urine and giving 30 grains (2 gm) of sodium bicarbonate each hour while the urine was below a *p*H of 7 0 and the same dose every two hours when the urine reached a *p*H of 7.0, when the urine became alkaline to phenolsulfonphthalein (*p*H 7.8) the administration of the bicarbonate was suspended. This was continued for four or five days

4. It is important to keep the eyes covered until all visual and retinal changes have disappeared.

It is believed that the use of ethyl alcohol in treatment has a favorable influence through interference with the oxidation of methyl alcohol Røe felt it not necessary to give ethyl alcohol when one is able to give bicarbonate under constant control as in the scheme of treatment above outlined But when this is not feasible, as for example during a long transport to hospital, he strongly advocated treatment with ethyl alcohol, giving gin, brandy, whiskey, etc, in an initial dose of 130 cc. and doses of 20 cc. every hour thereafter in the event that guided bicarbonate therapy is not practicable. Chew *et al* gave their patients one ounce (30 cc.) doses of whiskey every four hours for a day or two.

In the cases of Chew *et al.* response to treatment was usually prompt, as indicated both by clinical and laboratory criteria. Within a few hours dyspnea,

[illegible]

peared normal. The four exceptions showed a slight degree of retinal edema and had a slight diminution of central vision insufficient to interfere with their duties; in three months after discharge two of these four patients regained apparently normal vision and fundi Four of the five men who died were comatose and critically ill on admission to hospital, the fifth being conscious on admission but lapsing into coma very shortly. They were all intensely cyanotic and had pronounced respiratory embarrassment, did not respond to therapy, and died in respiratory failure within three hours after admission.

ACETANILID, ANTIPYRINE AND PHENACETIN POISONING

Acute cases of poisoning with any one or a combination of these drugs are

[illegible]

the unique outbreak of this type of poisoning reported by Scott *et al* (1946), all the thirty-five newborn babies in a nursery developed relatively mild degrees of dye poisoning as a result of being swathed in diapers that were used without washing after being stamped with an ink containing an aniline dye Other such instances have occurred, and in fact it seems that the first such outbreak was reported as long ago as 1886. Jones and Brieger (1947)

[illegible]

cyanosis, clammy sweat, cold extremities and a subnormal temperature.

THERAPY

In the severely poisoned patient of Jones and Brieger (1947), gastric lavage was performed, parenteral fluid was administered, repeated enemas and laxatives were given, the patient was kept in an oxygen tent for thirteen and a half hours. The child was able to be discharged from the hospital forty-eight hours after admission, but she was below normal in general activity and health for at least two weeks following the poisoning episode. Ascorbic acid has a number of times been used successfully in combating methemoglobinemia. Carnrick *et al.* (1946) found this agent far more desirable for the purpose than

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SALICYLATE POISONING

(*Note:* Other aspects of this subject are discussed in Rheumatic Fever)

The general toxic effects of excessively high dosage of sodium salicylate, phenyl salicylate (salol), acetylsalicylic acid (aspirin), and methyl salicylate (oil of wintergreen) are the same. In most instances the symptoms develop and progress rather slowly but this is not invariable; the most characteristic

they are quite severe and sometimes blood is vomited; in some cases there are several degrees of fever. Bowen *et al.* (1936) pointed out the ease with which this type of poisoning can be mistaken for diabetic acidosis. Mortality is very high, three of the four cases reported by Troll and Menten (1945) proved fatal. Fatalities have followed the taking of 300 grains (18 gm.) of aspirin, but Hopkins (1945) reported an instance in which 1250 grains (81 gm.) had been survived; 4 cc. of the oil of wintergreen have killed an infant, 6 cc. have been fatal to an adult.

THERAPY

It is very likely that in efforts directed toward the combating of hyperventilation, the maintenance of renal function and the promotion of salicylate excretion through the kidneys—all accomplished through the intravenous

intoxication in infants and young children reported by Erganian *et al.* (1947), glucose solution was given in addition to the alkali by intravenous and subcutaneous routes until oral feeding could be resumed. Vitamin C was also given to all of the patients, and in addition to parenteral vitamin K small whole blood transfusions were used to combat hemorrhagic tendencies.

COCAINE POISONING

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THERAPY

Prevention of Absorption.—If cocaine has accidentally been injected subcutaneously, the quick application of a tourniquet above the site of injection, if this has been in one of the extremities, may be life-saving; the pulse should not be completely obliterated.

Stimulants.—Cocaine is relatively rapidly destroyed, or at least rendered

unpleasant occurrences

Barbiturates.—Based upon the laboratory experiments of Tatum and his associates some years ago, the use of the barbiturates both in prophylaxis and treatment of cocaine poisoning has become quite general. The drug is usually given in ordinary or perhaps slightly larger dosage one-half hour before the use of the cocaine is to begin. In cases in which signs of poisoning have already appeared the soluble sodium barbiturate salts are injected subcutaneously or intramuscularly. Alwall (1941), in Sweden, on the basis of his own experience in fc

such

has

add to the succeeding period of deep cocaine depression. During the period of stimulation morphine is absolutely contraindicated because it will certainly add to the subsequent respiratory depression.

METHYL CHLORIDE POISONING

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(see Poisons Causing Stupor for list) Herzfeld reported some years ago that the ingestion of 1 to 2 ounces (30–60 cc.) of whiskey or brandy, ten to thirty minutes before the employment of cocaine, was very effective in preventing unpleasant occurrences.

Barbiturates.—Based upon the laboratory experiments of Tatum and his associates some years ago, the use of the barbiturates both in prophylaxis and [illegible]

in four cases of acute poisoning, advised the use of a quick-acting barbiturate such as pentothal, because after the preliminary period of great stimulation [illegible]

add to the subsequent respiratory depression.

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Colicky pain is usually controlled by 2 drachms (8 cc.) of paregoric every two hours for 2 or 3 doses; occasionally it will be necessary to give a single hypodermic of $\frac{1}{8}$ grain (8 mg.) of morphine sulfate, or 1/48 grain (1.3 mg.) of dilaudid, combined with 1/120 grain (0.5 mg.) of atropine sulfate.

These patients are often very much depressed and need support; however, in these cases the following are possibly better to use than the true "stimulants" listed in Poisons Causing Stupor: whiskey, $\frac{1}{2}$ to 1 ounce (15–30 cc.) to be sipped well diluted; aromatic spirits of ammonia, $\frac{1}{2}$ drachm (2 cc.) well diluted.

Feeding with soft foods may be cautiously begun within twelve to twenty-four hours. It is usually advisable to continue the bismuth subcarbonate in doses of 15 grains (1 gm.) three times daily for several days.

The testimony regarding the efficacy of the sulfonamides, both in shortening the acute attack and terminating the carrier state, is entirely conflicting.

BOTULISM

Botulism is acute poisoning caused by the toxin of *Clostridium botulinum*, an organism whose spores are widely distributed in nature, being found in the soil, on fruit and vegetables, in dust, in the intestinal tract of herbivorous animals and in the larvae of worms. The disease is caused by the ingestion of [illegible]

of the spores, however, does not give rise to symptoms. Eight per cent brine, or 50 per cent sugar concentration, inhibits the growth of the bacillus and prevents the formation of the toxin. In the latest tabulation I have seen there were listed 367 outbreaks of botulism in the United States between 1899 and 1943; the total number of cases during these forty-three years was 1052, the mortality rate 65 per cent. Most of the outbreaks have been due to the ingestion of foods improperly processed at home; it seems that with one possible exception no outbreak has been traceable to commercially canned foodstuffs in nearly twenty years.

Symptoms do not usually appear until eighteen to thirty-six hours have elapsed. At first there is malaise associated with constipation and subnormal temperature. Gastro-intestinal symptoms are unusual and when they occur are seldom violent. Then dizziness, headache and disturbances of vision appear: scintillation, diplopia, mydriasis, blepharoptosis and loss of the light reflex. Swallowing becomes extremely difficult, the tongue coated and breath foul and the mouth excessively dry, and general muscular weakness comes on. I [illegible] but in others [illegible]

those who recover there are no permanent sequelae though convalescence is very slow. In two cases that I saw in July, 1946, there was pronounced euphor-[illegible]a at the height of the illness; both patients recovered.

THERAPY

The indications here are to empty the gastro-intestinal tract, [illegible] patient, relieve the discomfort and administer the antitoxin.

[illegible]

rational, since the poison has been taken by the mouth, but what [illegible] pected from it is sufficiently indicated in the fact that the symptoms [illegible]

[illegible]

picrotoxin definitely increases the severity of the symptoms; after [illegible] has set in the drug may probably be used with safety and good effect [illegible] would only add to the discomfort at any time.

[illegible]

ploying this drug, in view of the sweat and depression that it [illegible] carefully weighed in each case.

Antitoxin.—The intravenous dosage is not less than 10,000 [illegible] repeated as indicated by the nature of the case. Geiger (1937) [illegible] was some advantage in giving the antitoxin in 1000 cc. of 10 per [illegible] solution, repeating the dextrose infusion without the antitoxin [illegible] several s[illegible] that by [illegible] for the a[illegible] it seemed to be strikingly effective though the diagnosis was [illegible]

MUSHROOM POISONING

In practically all cases of mushroom poisoning there are [illegible] of gastro-intestinal disturbance: nausea, vomiting, gastric pain, [illegible] addition, depending upon the species of mushroom ingested, [illegible] any of the following symptoms: nephritis with anuria or [illegible] jaundice; excessive perspiration, salivation and lacrimation; [illegible] pupils, mental confusion, excitement, convulsions, coma and [illegible]

THERAPY

The stomach should be emptied by the use of any of the [illegible]

[illegible]

[illegible] insomnia).

SHELLFISH POISONING

During certain seasons of the year the mussels and clams in some localities contain a powerful neurotoxic poison that causes death by respiratory paralysis in a rather high proportion of the persons affected; Sommer and Meyer (1941), who determined that the poisoning is due to the presence of the dinoflagellate, *Gonyaulax catenella,* recorded that 346 cases had occurred on the Pacific Coast since 1927 with twenty-four deaths. Cases have also been reported in Japan, Germany, France, Scotland and Norway. Patients who do not have the fatal paralytic form of the disease may experience gastro-enteritis with nausea, vomiting and diarrhea, or they may experience nervous symptoms accompanied by diffuse erythema, urticaria, angina and dyspnea; the latter forms of the malady are usually not fatal.

THERAPY

No specific treatment or antidote for mussel poisoning has been developed. *Of course the aim should be to empty the gastro-intestinal tract as rapidly as* possible; Sommer and Meyer said that during the 1939 outbreak the provocation of active vomiting by the use of apomorphine was more effective in removing pieces of shellfish from the stomach than lavage. Mussel poison is strongly adsorbed on charcoal, Lloyd's reagent and similar adsorbents. Alkaline fluids are said to be indicated considering the instability of the poison in an alkaline medium. Of course in severe cases artificial respiration has to be resorted to.

MILK SICKNESS

This is a very old scourge in the United States, having been known apparently to [illegible]
frontier
attacked [illegible]
and from which birds and beasts of carrion that fed upon their carcasses were said to have died also. Hull (1941), however, has cast some doubt upon the latter statement for he says that, at least in man, the disease can be contracted only from ingesting milk, butter or cheese from afflicted cattle. Pasteurization of these dairy products is not protective. We now know the cause to be the ingestion by the animals of one or the other of two weeds: white snakeroot and rayless goldenrod. The symptoms in man are. violent vomiting, pain and stiffness in the legs, low blood pressure and extreme weakness, obstinate con- [illegible]

[illegible]

but Hardin stated, in 1934, that she had treated more than 100 cases in the preceding sixteen years in North Carolina, Gowen (1938) reported 21 cases occurring in four outbreaks in Illinois in 1936 and 1937, and Hull (1941) stated that there probably occur under normal conditions "not more than [illegible] ...y of
... the
...ting

THERAPY

The studies of Bulger *et al.* (1928), in animals poisoned by white snakeroot, indicated that some of the symptoms might be caused by the marked ketosis, lipemia and profound hypoglycemia that they observed. Hardin (1934) found [illegible] the majority of patients treated without alcohol in some form died. Alcohol administered to the point of intoxication was the best antidote.

LEAD POISONING

The first symptoms of lead poisoning are usually abnormal fatigue accompanying irritability and sleeplessness, headache, loss of appetite and vague nausea and body pains. Constipation and increasing muscular weakness, especially of the extensors of the right hand, become marked, and then there appears tremor of the mouth and eye muscles, the latter detectable when the patient lowers the lids. Tremor of the extended fingers usually appears somewhat late, as do also actual radial paralysis and colic. During the colic—which is caused by tonic stimulation of the intestinal musculature by the direct action of the lead so that there is a contraction ring with an area of high pressure due to increased peristalsis above—the severe pains are located below the umbilicus in a scaphoid abdomen, and in contrast to appendicitis and peritonitis there is no tenderness and the suffering is relieved by pressure. The writhing of the intestines is often clearly to be felt. Frequently there is a desire to vomit and to defecate, but very little comes of this; obstinate constipation is certainly the rule, though diarrhea is on record. The patient sweats and the temperature and pulse rate are much decreased; a rise in blood pressure and blood sugar is usual but not invariable. There is also an apparent inability of the vessels to relax, which accounts for the marked pallor and the slow hard pulse as well as the hypertension, this may also give rise to sudden but usually temporary attacks of blindness (the contractions can sometimes be seen in the retinal and conjunctival vessels), occasionally to contracted kidney in protracted cases, to angina pectoris and gangrene of the extremities, and, together with a direct poisoning of the brain cells, to encephalopathy, manifested in hallucinations, babbling, delirium, or stupor. Whether the peripheral paralyses due to lead are of neuritic, muscular, spinal, or vascular causation is not known. Sterility and miscarriage as accompaniments of the malady were recognized many years ago. The intensity of the lead line on the gums depends much upon the state of the mouth. Death is nowadays unusual but there may be degenerative neurologic sequelae of a most distressing sort, particularly in children, probably as a result of prolonged increase in intracranial [illegible] below 65 per cent. A moderate lymphocytosis is seen in some cases, perhaps a slight increase in monocytes also.

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MILK SICKNESS

This is a very old scourge in the United States, having been known apparently to the Indians, but it has never appeared anywhere else. In the early frontier days, cattle browsing in uncleared land and wild pastures were often attacked by a peculiar disease known as "trembles," from which they died, and from which birds and beasts of carrion that fed upon their carcasses were said to have died also. Hull (1941), however, has cast some doubt upon the latter statement for he says that, at least in man, the disease can be contracted only from ingesting milk, butter or cheese from afflicted cattle. Pasteurization of these dairy products is not protective. We now know the cause to be the ingestion by the animals of one or the other of two weeds: white snakeroot and rayless goldenrod. The symptoms in man are: violent vomiting, pain and in the legs, low blood pressure and extreme weakness, obstinate con-

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stated that there probably occur under normal conditions "not more than fifty cases" in Illinois each year. It is a fact of no little interest that many of the apparently purposeless peregrinations of the Lincoln family during the boyhood of the future President were in reality flights from this blighting affliction. Lincoln's mother, and at least three of his close kin, died of it.

resorted to abroad than in this country is the observation of a much increased coproporphyrin content in the urine. So far as absorption, storage and elimination are concerned, it has been shown that the metabolism of lead and of calcium is closely related, but the minutiae of these processes are not yet understood. The question of delayed callus formation in lead-poisoned individuals suffering fracture has been raised, and one school believes that there is injury to the calcium-secreting osteoblasts with actual bone necrosis as a possibility; some, but not all, observers feel that the high incidence of arthritis and analogous conditions also reflects bone injury

lead colic." Not until the eighteenth century was the entity given scientific status, however, a service performed by Sir George Baker (1722–1809), who got himself denounced as a faithless son of his county for showing that Devonshire colic was due to the lead in Devonshire cider. Today, lead poisoning ranks first among the industrial diseases, and epidemics are also not of infrequent occurrence; in 1930 there were serious outbreaks in two Continental cities whose water is conveyed in lead pipes. Bizarre, indeed, are some of the ways in which we can take harmful amounts of lead into the body, but there is no space here for the list. Reznikoff (1943) said that Negroes are much more susceptible to lead poisoning than whites and that alcoholism also predisposes.

THERAPY

After prevention of the possibility of further absorption of lead by whatever means are required in the individual case, the treatment is divided into two

severe acute manifestations calcium is given because as calcium is stored in the bones lead is stored also, as was shown by Aub, Hunter and their associates, in 1925. Practically instant relief is brought by the intravenous administration of solutions of calcium salts, patients often going at once to sleep though some

through the use of cathartics for a considerable period of time in order to remove the relatively large quantity of lead that is probably present in the tract. The calcium injection may be safely repeated if the spasm returns, as it usually does several times in the more severe cases; some men routinely repeat every three or four hours for the first twenty-four to forty-eight hours and three to

10 cc. of a

5 cc. of a 10

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With regard to stippling of the erythrocytes, one may make the following statements: (a) There may be stippling which indicates only absorption of lead without clinical poisoning, but, with the exception to be noted, there is no lead poisoning entirely without stippling; the exception, emphasized by the Committee on Lead Poisoning of the Industrial Hygiene Section of the American Public Health Association (1943), is the very acute type of lead intoxication following promptly upon a massive exposure to lead compounds, such as the acute encephalopathy of tetra-ethyl lead poisoning, or the acute and per-

face of known lead exposure, often indicates abnormal lead absorption, though Machle (1947) stated the opinion in the Seventh Annual Congress on Industrial Health that no critical stippled cell level for hazardous lead exposure can be set Movitt (1945) said that when basophilic stippling cannot be found in the peripheral blood to a significant extent it may frequently be seen in

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is also leukocytosis, the other types of metallic poisoning, benzene poisoning, diseases of the blood-forming tissues and malaria must be ruled out.

The Committee took the position that abnormal lead findings in the tissues, blood, cerebrospinal fluid, urine or feces mean only that there has been an abnormal lead absorption and thus tend to reveal the existence and the degree of severity of lead exposure, but they do not demonstrate the existence of lead poisoning It was stated that the large proportion of cases of lead poisoning ... tion show concentrations between 0.15

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occupation group exceeds the latter value evidence of lead intoxication can be found among them before long. He felt that where "spot" samples of urine ... the most helpful

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in the results obtained in the summer and in the winter, in temperate and in semi-tropical climates.

Normal blood lead values were placed by the Committee in the range between 0 01 and 0.06 mg. per 100 gm. of whole blood with only occasional values in excess of 0.04 mg (Kehoe's, 1947, figures were 0 01 or slightly less and 0.055, only an occasional sample exceeding 0.05); it was stated that find-

... determination except in very rare instances of overwhelming ...

quately determined

(0.3–1 gm.) of potassium iodide three times daily, often considerably increased if well borne by the stomach; (d) sodium bicarbonate, 5 to 8 drachms (20–30 gm.) daily, divided into five or six portions.

Belknap, of Milwaukee, whose industrial experience has been very large, [illegible] cells) and have remained there for two or three weeks, and finally until the lead in the twenty-four-hour urine is 0.15 mg. or lower. These precautions insure that no great amount of lead is freshly liberated from the skeleton to be superimposed on lead still freely circulating throughout the blood.

It is usual practice to continue a course of ammonium chloride supplementation to a calcium-poor diet for about a month to constitute a course of deleading, and then a period of a month or so in which the patient is on a full-rounded diet high in calcium, phosphorus and vitamins should intervene before another deleading course is instituted. However, Belknap said that he does not find it practical to use ammonium chloride and sodium bicarbonate or a low calcium diet to delead men who are actually at work. He prefers to delead for a period of only a few days at a time, using 15 drops of the saturated solution of potassium iodide twice a day and by this means gently stimulating lead [illegible] 0.2 mg., and the likelihood of recurring toxic episodes of lead poisoning is therefore very slight.

As most of the lead is eliminated through the bowel, the giving of saline cathartics, particularly magnesium sulfate, is considered to be especially important; senna, cascara and other drugs that may cause a more spasmodic type of movement are contraindicated, but later in the treatment mineral oil may be substituted for the salines.

Treatment of Complications.—The anginal symptoms and the peripheral vascular spasmodic disturbances are treated with the xanthine diuretics as usual. In the treatment of the paralyses, months of patient massage, active [illegible] by either Evans *et al.* (1943) or Cantarow and Trumper (1944).

BENZOL POISONING

[illegible] and finally death through respiratory paralysis But chronic benzol poisoning is assuming a position of some importance in industries in which the workers

edly). The injections always must be given very slowly—taking four or five minutes—to avoid severe nausea and vomiting; furthermore, rapid administration may cause acute paralysis of respiration and circulation. Even at best there is usually a fall of 10 to 40 mm. in the blood pressure due to peripheral vasodilatation, and the patient feels as though his entire body were on fire. During the time that injections are being given, Belknap also gives 75 grains (5 gm.) of calcium gluconate in milk three times daily after meals. The diet should be alkaline: fruits, vegetables and milk; as little meat, fish, eggs and cereals as possible.

In the presence of serious cerebral symptoms it has been found advisable to use barbiturates in preference to morphine to control the excitement and convulsions, and the use of hypertonic saline solution with glucose is indicated to combat dehydration and exhaustion; perhaps the injection of 50 cc. or more of a 50 per cent sucrose solution may be indicated to combat cerebral edema.

Kety and Letonoff (1943) reported the successful control of symptoms in a

large doses of sodium citrate by mouth is extremely disagreeable and it seems to me unlikely that the citrate treatment will replace the calcium treatment. Cantarow and Trumper (1944) said that in their experience the most satisfactory results are obtained by the use of sodium citrate in addition to the use of calcium.

Elimination of the Lead.—The students of lead poisoning are divided into two camps on the question of deleading, the one group maintaining that so long as there is a considerable body of lead stored in the body the patient is in danger of recurrence of lead intoxication during such illness as acute infections, alcoholic excesses, surgical procedures, etc., and that it is therefore wise to eliminate the lead as expeditiously as possible consistently with safety. The other group feels that recurrence of lead poisoning without further lead exposure is rare after the complete subsidence of the episode of intoxication, that the excessive quantities of lead are eliminated spontaneously from the body, and that the current methods of deleading do not remove lead from the body at a materially increased rate or to a practically important degree. I shall, however, describe here the methods of deleading, which simply consist in

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the diet). In addition deleading agents are given: (a) ammonium chloride, starting with 15 grains (1 gm.) three times daily during meals (one may either direct that three 5-grain enteric-coated tablets be taken with a meal or that a teaspoonful of a 20 per cent solution be dissolved in a full glass of water and be sipped with the meal) and increasing dosage so that after a week or so 90 to 30 minims
—adminis-
o 15 grains
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(0.3–1 gm.) of potassium iodide three times daily, often considerably increased if well borne by the stomach; (d) sodium bicarbonate, 5 to 8 drachms (20–30 gm.) daily, *divided into five or six portions.*

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Kety and Letonoff (1943) reported the successful control of symptoms in a small group of patients through the administration of sodium citrate, the drug being given in 4 or 5 gm. doses dissolved in one ounce of water, three or four times daily; four patients with severe colic on admission received 50 cc. of a sterile 2.5 per cent aqueous solution by vein. The *in vitro* studies of Mortensen ... or a carrier taking up ...

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THERAPY

The stomach must be lavaged of course as soon as possible; it is probably wise to employ 1:5000 potassium permanganate solution for the purpose since this agent will convert yellow phosphorus into harmless phosphates. Since Atkinson showed in experimental studies a number of years ago that the administration of liquid petrolatum either before or after feeding phosphorus would save experimental animals through solution of phosphorus in the oil, it is probably advisable to leave several hundred cubic centimeters of liquid petrolatum in the stomach after completing the lavage.

In every case of course it must be assumed that some absorption has taken place; therefore one must attempt to protect the liver and the kidneys, which are the organs most severely damaged by the phosphorus. In a very severely poisoned patient who recovered, LaDue *et al.* (1944) gave 2000 cc. of 10 per cent glucose intravenously immediately after completing the lavage and repeated this at least once daily for the first ten days. An eggnog mixture containing 60 gm. protein, 300 gm. carbohydrate and 30 gm. fat was also given each day by duodenal intubation, vitamin concentrates and 2 oz. of mineral

SNAKE BITE

The total number of deaths annually throughout the world from the bites of poisonous snakes is probably between 25,000 and 35,000 of which 20,000 to 25,000 occur in India alone. The other cases are scattered throughout all the rest of the world, few regions being without one or more dangerous families

several vipers, the daboia, the habu, the cobra, the king cobra, the krait; *Africa*, the vipers, the puffadder, the asp, the mamba; *Oceania*, brown snake, black

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of the serious bites in Central America, but the bushmaster, a heavier viper, bears a worse popular reputation), the copperhead, the water moccasin, the rattlesnakes, and the coral snake, the latter also occurring in the West Indies.

The symptoms of poisoning vary with the different snakes; I have drawn

speech and progressive muscular paralysis; respiratory death. *King Cobra:* little or no local reaction; difficult and stertorous respiration; patient remains in a semi-conscious state until death from respiratory paralysis. *Krait:* rapid emaciation, progressive muscular weakness and other symptoms of slow intoxication; death after six or more days from respiratory paralysis. In Lumsden's

are exposed for long periods to relatively low concentrations of benzol fumes. In these cases the *hemorrhagic tendency is a predominating* characteristic, hemorrhages occurring into the skin and all the mucous membranes and in the most severely affected patients even into the serous membranes and the

basophilia; it is said that in very severe cases no reticulocytes at all are to be found.

THERAPY

In cases of acute poisoning the patient is of course to be got out into the

animal charcoal followed by the free administration of animal charcoal and magnesium sulfate solution by mouth. In the chronic cases the patient is put to bed, given a full diet, and transfused with whole blood as often as seems practicable. Liver and iron are also given in large amounts. Wilson (1942) recommended in addition large daily doses of calcium, phosphorus, yellow bone marrow and multiple vitamins. In the belief that the spleen has inhibiting effect on the bone marrow, splenectomy is sometimes resorted to in desperately ill patients, but I am unable to cite any statistical evidence of its efficacy.

IVY POISONING

(See in *Eczema-Dermatitis*)

PHOSPHORUS POISONING

In lands, particularly in the Far East, where the sale of matches made from yellow phosphorus is still permitted, most cases of phosphorus poisoning are due to the chewing of matches by children, but in the United States practically all of the cases result from the ingestion of roach or rat paste or fireworks. *This type of poisoning is not frequently* encountered in our country; still, (1944) reported that sixteen patients had been treated for phos-

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THERAPY

In cases of acute poisoning the patient is of course to be got out into the fresh air as soon as possible and he must be given artificial respiration and

mouth it is of value to wash out the stomach with a 3 per cent suspension of animal charcoal followed by the free administration of animal charcoal and magnesium sulfate solution by mouth. In the chronic cases the patient is put to bed, given a full diet, and transfused with whole blood as often as seems practicable Liver and iron are also given in large amounts. Wilson (1942) recommended in addition large daily doses of calcium, phosphorus, yellow bone marrow and multiple vitamins. In the belief that the spleen has inhibiting effect on the bone marrow, splenectomy is sometimes resorted to in desperately ill patients, but I am unable to cite any statistical evidence of its efficacy.

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sions, combined with a history of the ingestion of phosphorus and the recovery of phosphorus from the luminous vomitus or stools, makes diagnosis easy; in the absence of a history of the ingestion of vermin or rat poison or fireworks, however, the cases can be quite baffling. The liver is usually enlarged and the blood sugar level is low as a reflection of failure of glycogenolysis; in Chretien's (1945) patient the white cell count fell to 1200. The symptoms in phosphorus poisoning may appear within a few hours or not until several days after the poison has been taken.

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(1946) report of a bite suffered under peculiarly interesting circumstances the patient died in approximately three hours from the time of being bitten. *Daboia:* intense local reaction, ecchymosis and hemorrhages; nausea, vomiting and collapse with rapid weak pulse; if death is not immediate, hematuria and albuminuria, anemia, intense emaciation, and then death. *Fer-de-lance, habu:* immediate local edema that spreads rapidly, ecchymosis, severe pain and hemorrhage at site of bite; parched throat, thirst, congestion, hemorrhages into the mucous membranes and even through the skin, albuminuria, death in toxic exhaustion. According to Sonneborn (1946), the symptoms resulting from the bite of the habu on Okinawa during War II were not nearly so severe [illegible] n doctors told them that only [illegible] f the bite; Martin (1946) said [illegible] were there any effects on the respiratory or other brain centers. *Rattlesnake:* local pain, hemorrhage, ecchymosis, gangrene; rapid general symptoms (I once saw a young Negro lad vomiting and profusely sweating twenty minutes after I had seen him bitten [illegible] nausea, and [illegible] es until early [illegible] rhead do not seem to be among the most poisonous snakes; also a bite by the true water moccasin (not the maligned, though vicious, common water snake) is quite rare. *Coral:* no local evidences except intense pain, salivation and lacrimation; depression, somnolence, convulsions, death in collapse. *Tiger, death-adder, brown, black, taipan:* regarding this group of snakes of Australia and the Southwest Pacific, Kellaway (1942) wrote that there is nausea and vomiting, blanching of the skin and sweating, drowsiness, rapid shallow pulse and respiration, many neurotoxic symptoms except in the case of the black snake, [illegible] sometimes hemoptysis, hemateme- [illegible] owing [illegible] r col- [illegible] con- [illegible] assive edema up to the [illegible] most pronounced in the neighborhood of the main lymphatic trunks In about half the cases reported to him the general symptoms (gastro-intestinal and respiratory disturbances, swelling of lips, face and tongue) were severe enough to occasion real anxiety for the patient's life, but in most cases the critical period was of brief duration and the patient out of danger within twelve hours.

THERAPY

[illegible]

gangrene below the level of the tourniquet [illegible] soon as the tourniquet has been applied, to enlarge the wound with crucial incisions 1 inch or more across and begin sucking out the venom, sucking for alternate fifteen-minute periods for many hours, the tourniquet having been removed after eight hours. However, Clark (1942), discussing his experience of snake bite during many years in Central America and regions contiguous to the Canal Zone, said that such incisions are unlikely to expose the areas in which venom has been deposited since the fang is curved and the deposition

of venom is not made directly beneath the fang marks; furthermore, incisions that do happen to pass through venom droplets only increase the areas of raw surface through which rapid absorption may take place. Clark advocated simple vigorous sucking of the wound for five minute periods at frequent intervals and removal of the tourniquet one hour after the antivenin has been administered. Maegraith (1945) strongly made the point that since so many snakes, particularly the African cobras, dribble and spray their poison over the surface of the area bitten, cuts in the region of the bite must never be made until the area concerned has been well washed (with urine or sputum if no water is available) to remove venom from the surface, for cutting in the region of an unwashed bite amounts to a possible further introduction of venom into the tissues.

Ahuja and Brooks (1945), in testing the action of many substances against cobra venom in experimental animals, found that a 5 per cent emulsion made with familiar Lifebuoy carbolic soap was quite effective in combating the venom when infiltrated at the site of the inoculation They therefore recommended that injections of 0.5 to 1cc at points surrounding the bite, to a total of 5 cc., might well be tried in cases of bites in man and invited reports from anyone making such trials It seems possible to me that this might be a very good contribution and that trials of the method are certainly in order. The soap solution must of course not be injected intravenously and not in any [illegible] is suggested purely as a

[illegible] ovocaine block rendered [illegible] venom of the European [illegible]

depending upon the site of the bite.

Antivenin Treatment.—Obtain the antivenin at once and inject half of an ampule subcutaneously around the site and the remainder intramuscularly—in fulminating cases intravenous injection is permissible Doses are doubled for children because the smaller the body the greater the proportionate amount of venom in the tissues. Repeat injections at one- to two-hour intervals unless and until symptoms are markedly diminished.

In North America.—The serum is polyvalent against the venoms of rattlesnake, water moccasin and copperhead It is marketed in 15 cc vials and is known as "Antivenin (Nearctic Crotalidae) Polyvalent." The problem of getting this antidote to the victim, who has probably limped into some isolated [illegible]

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THERAPY

Immediate Surgical Treatment.—Apply a tight bandage above the knee in bites on the lower extremity, above the elbow in bites of the upper extremity; release for a few seconds at ten- or fifteen-minute intervals in order to prevent gangrene below the level of the tourniquet. Traditionally it is the custom, as soon as the tourniquet has been applied, to enlarge the wound with crucial incisions 1 inch or more across and begin sucking out the venom, sucking for alternate fifteen-minute periods for many hours, the tourniquet having been removed after eight hours. However, Clark (1942), discussing his experience of snake bite during many years in Central America and regions contiguous to the Canal Zone, said that such incisions are unlikely to expose the areas in which venom has been deposited since the fang is curved and the deposition

of venom is not made directly beneath the fang marks; furthermore, incisions

vals and removal of the tourniquet one hour after the antivenin has been administered. Maegraith (1945) strongly made the point that since so many snakes, particularly the African cobras, dribble and spray their poison over the surface of the area bitten, cuts in the region of the bite must never be made until the area concerned has been well washed (with urine or sputum if no water is available) to remove venom from the surface, for cutting in the region of an unwashed bite amounts to a possible further introduction of venom into the tissues.

Ahuja and Brooks (1945), in testing the action of many substances against cobra venom in experimental animals, found that a 5 per cent emulsion made with familiar Lifebuoy carbolic soap was quite effective in combating the venom when infiltrated at the site of the inoculation They therefore recommended that injections of 0 5 to 1cc. at points surrounding the bite, to a total of 5 cc., might well be tried in cases of bites in man and invited reports from anyone making such trials. It seems possible to me that this might be a very good contribution and that trials of the method are certainly in order The soap solution must of course not be injected intravenously and not in any sense be used as a substitute for antivenin; its trial is suggested purely as a first aid measure.

Taoubes (1941), in Russia, thought that circular novocaine block rendered the nervous system insusceptible to the action of the venom of the European

Antivenin Treatment.—Obtain the antivenin at once and inject half of an ampule subcutaneously around the site and the remainder intramuscularly—in fulminating cases intravenous injection is permissible Doses are doubled for children because the smaller the body the greater the proportionate amount of venom in the tissues. Repeat injections at one- to two-hour intervals unless and until symptoms are markedly diminished.

In North America.—The serum is polyvalent against the venoms of rattlesnake, water moccasin and copperhead It is marketed in 15 cc. vials and is known as "Antivenin (Nearctic Crotalidae) Polyvalent " The problem of getting this antidote to the victim, who has probably limped into some iso-

being extensively and effectively used in Central America since the development of the snake farm for collection of venoms at Tela, Honduras. Clark (1942) said that it is effective against the bites of all the more usual poisonous snakes of the region except the tropical rattlesnake, the bushmaster and the coral snake.

(1946) report of a bite suffered under peculiarly interesting circumstances the patient died in approximately three hours from the time of being bitten.

hemorrhage at site of bite; parched throat, thirst, congestion, hemorrhages into the mucous membranes and even through the skin, albuminuria, death in toxic exhaustion. According to Sonneborn (1946), the symptoms resulting from the bite of the habu on Okinawa during War II were not nearly so severe as had been anticipated; he said that Okinawan doctors told them that only the very young or very debilitated ever died of the bite; Martin (1946) said that in none of the soldiers bitten on Okinawa were there any effects on the respiratory or other brain centers. *Rattlesnake:* local pain, hemorrhage, ecchymosis, gangrene; rapid general symptoms (I once saw a young Negro lad vomiting and profusely sweating twenty minutes after I had seen him bitten by a large diamond-back) consisting of rapid and weak pulse, nausea, and vomiting, sometimes diarrhea, cold sweats, and a series of collapses until early death takes place The pygmy rattler and the American copperhead do not seem to be among the most poisonous snakes; also a bite by the true water moccasin (not the maligned, though vicious, common water snake) is quite rare. *Coral:* no local evidences except intense pain, salivation and lacrimation; depression, somnolence, convulsions, death in collapse. *Tiger, death-adder, brown, black, taipan:* regarding this group of snakes of Australia and the Southwest Pacific, Kellaway (1942) wrote that there is nausea and vomiting, blanching of the skin and sweating, drowsiness, rapid shallow pulse and respiration, many neurotoxic symptoms except in the case of the black snake, such as drunken gait, slurring speech, etc., sometimes hemoptysis, hematemesis and hematuria, and death from respiratory paralysis sometimes following convulsions. *Adder.* According to Walker (1945), the degree of shock or collapse varies greatly in different cases whereas the local reaction is most con-

to him the general symptoms (gastro-intestinal and respiratory disturbances, swelling of lips, face and tongue) were severe enough to occasion real anxiety for the patient's life, but in most cases the critical period was of brief duration and the patient out of danger within twelve hours.

THERAPY

Immediate Surgical Treatment.—Apply a tight bandage above the knee in bites on the lower extremity, above the elbow in bites of the upper extremity; release for a few seconds at ten- or fifteen-minute intervals in order to prevent gangrene below the level of the tourniquet. Traditionally it is the custom, as soon as the tourniquet has been applied, to enlarge the wound with crucial incisions 1 inch or more across and begin sucking out the venom, sucking for alternate fifteen-minute periods for many hours, the tourniquet having been removed after eight hours However, Clark (1942), discussing his experience of snake bite during many years in Central America and regions contiguous to the Canal Zone, said that such incisions are unlikely to expose the areas in which venom has been deposited since the fang is curved and the deposition

pulse, the blood and spinal fluid pressures are usually above normal.
The vast majority of the victims of this spider recover in a few days but in occasional instances paresthesias and muscular spasms and weakness persist for several weeks or even months

THERAPY

The acute symptoms of spider bite are so severe as to necessitate immediate efforts at alleviation. Resort is practically always had to the opiates, though all observers agree that these patients can tolerate very large amounts without deriving much relief from them Hot baths are often found helpful; Blair (1934), who permitted himself to be experimentally bitten, obtained his best relief in this way, and Walsh and Hargis (1935) found baths very useful in their series of cases. Magnesium sulfate, given intravenously in dosage of 20 cc. of 10 per cent solution, repeated as necessary to overcome spasticity and hypertension, has been repeatedly reported upon favorably, the most recent observer to praise it to my knowledge was Davis (1946). Bell and Boone (1945) said that their experience failed to support the earlier claims of the therapeutic effectiveness of intravenously administered calcium salts. These latter observers, however, reported that a patient who was still in extreme pain six and one-half hours after the bite, despite the use of several sedatives and analgesics, experienced quick relief from the intramuscular injection of 2 cc. of 1:2000 prostigmine methylsulfate and 1/150 grain (0.4 mg) of atropine sulfate. The use of convalescent serum has not given consistently good results nor has spinal drainage.

An antitoxic serum prepared by immunizing horses against the venom of L. mactans is now Council-accepted; the serum is injected intramuscularly in a dosage of 2.5 cc. Lashley (1946) kindly informed me that in the three cases in which he used the serum it was wonderfully effective, the patients being relieved of their symptoms within thirty minutes. However, since spider bite carries no threat to life and serum sickness is often a protracted and occasionally possibly even a serious malady, it is advisable to test for the patient's sensitivity to horse serum before using this antivenin; the packaged material contains a vial of normal horse serum for performing such tests.

POISONING TREATED ELSEWHERE IN THE BOOK

The places throughout the book in which the toxicology of various drugs is dealt with are too numerous to list here. The reader is requested to look in the Index for the drug in which he is interested

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In Oceania.—Kellaway (1942) stated that the antivenin available in Australia is a monovalent one prepared by the use of tiger snake venom, but that it is so potent as to be useful in treating the bites of most of the Australian snakes except the brown snake Martin (1946) advised that in cases of habu bite, the North American (Nearctic) antivenin should be used, but I have seen no record of its employment.

In India —Despite the fact that Calmette's serum seems to be absolutely antidotal to cobra venom, its use can hardly have made even a faint impression on the mortality record in India. The working people, scattered in isolated villages over an enormous territory, often sleep out at night and thus fall easy victims to the wandering cobra that, seeking its meal of snakes, finds the sleeping native and wantonly bites him. There is little hope that serum will ever be sufficiently well distributed that its administration will become possible to many of these unfortunates soon enough to save their lives. Wyon (1945) reported the employment of an antivenin in four cases of Russell's viper bite, but earlier reports had cast some doubt upon the value of this antivenin

In South America.—We know practically nothing, of course, of the incidence of fatal snake bite in the wilds of this continent, but on the large estates and industrial workings the conditions are more favorable for treatment than in India. The working population, while scattered through the forests, particularly in the north, is more or less concentrated about the haciendas, making it easy to see the victims promptly and provide efficient care; it has been stated that the antivenins are being used successfully under these circumstances

In England —The experiences of both Batt (1944) and Williams and Davies [illegible]

possibly serve to dilute the toxin. Blood transfusion and oxygen administration is indicated The use of alcohol seems to lessen the patient's chance of recovery, popular opinion to the contrary notwithstanding

SPIDER BITE

In the United States practically all of the authenticated cases of arachnidism have been due to the bite of *Latrodectus mactans*, commonly known as black widow, shoebutton, hourglass, and T-dot spider. To Bogen is due great credit for reawakening interest in this subject, for it is only since he made his series of reports some years ago that the profession has become fully aware of the frequency of spider bite and the nature of the syndrome. Most of the victims have been males who were bitten on the penis or adjacent parts while sitting in an outdoor privy. The stinging pain of the bite soon subsides and there is usually little or no visible lesion; then, fifteen to thirty minutes later, pain reappears, usually at the site of the bite and spreads all over the body, reaching its maximum about an hour after the bite. There is generalized muscle spasm and very often a boardlike rigidity of the abdominal wall. The pain is agonizing but local tenderness is usually entirely absent, the patient usually

an infusion of 0.2 per cent novocaine and 5 per cent dextrose over a period of forty to sixty-five minutes; they were reported to have experienced practically [illegible] ior- [illegible] 15 per cent of the body surface will probably suffer from shock and that if the area is 25 per cent the shock will be fatal unless prompt and active treatment is given The mechanism of this serious secondary shock in the burned patient seems to be the following: as a result of the injury to capillaries through the burn there is a loss of plasma both into the burned tissues and by "weeping" from the skin, and later there may be generalized loss of plasma in the tissues remote from the burn site; the total loss may exceed several liters in a very short period of time Burn shock, then, is a state characterized by reduction in blood volume, cardiac output and blood flow, and hemoconcentration, and carrying with it the threat that the resultant anoxic damage to tissues will, as a result of its persistence, give rise to generalized increased capillary permeability of an irreversible type

Plasma and Electrolytes.—Levenson *et al.* (1946) said that in all cases of severe burns the treatment of shock should begin before dressing the burns, intravenous electrolyte and plasma being given simultaneously. The first dose of plasma is to be given rapidly and the first dose of electrolyte slowly unless [illegible] john), or Betasynplex (Winthrop). If the patient is intoxicated or in delirium tremens it is felt advisable to give five times the dose of ascorbic acid and of vitamin B complex. The plasma and electrolyte dosage recommended by this group are given in Table 25

Method of Administering Plasma.—Plasma is administered by gravity from the container through a tube and filter, the injection usually being into the convenient basilic vein. However, in some instances the arm veins may be collapsed and one will be obliged to enter the femoral vein. Another route of entry, drawn attention to by Tocantins a few years ago, is the sternal marrow The marrow cavity of the sternum is entered, under local anesthesia, by the introduction of a shortened stiff lumbar puncture needle through the skin and subcutaneous tissue and anterior lamella of the sternum until a sensation of give indicates that the needle has entered the marrow cavity; after withdrawing the stilet a small amount of marrow is aspirated before beginning the infusion. In children the marrow cavity of the tibia or femur is entered; Meola (1944) reported that his group had successfully given 326 infusions in this way to children.

Neither preliminary cross-matching nor skin testing is necessary before [illegible] unit of plasma as customarily prepared contains 1.2 gm. of citrate; since 15 gm of citrate given intravenously have been fatal, it follows that 6 units or 1500 cc. of pooled plasma bring one halfway to the possibly fatal dose of

BURNS, SHOCK, CRUSH AND BLAST SYNDROMES

BURNS

In the years since the outbreak of War II there has been much experience with burns and consequently an extensive reexamination of the principles of therapy; it is now possible to present the subject in a rationalized and much simplified manner.

GENERAL CARE IN MAJOR BURNS

Pain, Fear, Cold, Exhaustion.—The recently burned individual will most likely be suffering *very severe pain, he will have had a great fright* and may still be in a very fearful state, and if he has been involved in a general holocaust he may be in an exhausted condition and perhaps thoroughly wetted

sake may actually be harmful since the patient with the cold extremities of shock may be merely manifesting the compensatory phenomenon of conservation of blood volume for the vital centers; to attempt to warm up such a patient and produce vasodilatation may do serious harm. Burn tents with batteries of electric light have practically disappeared from hospitals, at least in this country.

According to Finland *et al.* (1946), almost all the patients admitted to the Boston City Hospital from the Cocoanut Grove fire required some sort of sedation immediately on arrival and for several hours or even days later, but they were not certain that some of these patients were not harmed indirectly by suppression of respirations or of the cough reflex through the use of morphine. They said that a consideration of individual cases left the impression that more than two or three doses of $\frac{1}{6}$ to $\frac{1}{4}$ grain (10 to 15 mg.) of morphine in a single day *were probably unnecessary;* the larger amounts were usually given in desperation to patients with some evidence of respiratory obstruction and in spite of the fact that no obvious benefit resulted. It was noted, by way of contrast, that when restlessness was due to pain alone *smaller doses were required* and relief was more rapid and lasted longer. In many cases the opiates were used in conjunction with barbiturates, bromides or aspirin and the combined effect was usually better than that obtained from the opiates alone. Levenson *et al.* (1946), in presenting an outline for the treatment of severe burns as the

butal) *may be given intravenously* in a dose of $1\frac{1}{2}$ grains (0.1 gm.), or 4 cc. of paraldehyde may be given intravenously.

Gordon (1943) reported his extremely interesting experience in the use of procaine (novocaine) *intravenously for control of pain* in burned soldiers in War II. Ten patients were so treated, in most instances receiving 300 cc. of

hemoglobinemia, which is usually the first forty-eight to seventy-two hours, this alkalinization can be accomplished by the intravenous injection of 3.75 gm. of sodium bicarbonate in addition to the electrolyte solution that is being administered in the direct attempt to combat shock. Later additional bicarbonate should be given only if the urine fails to become or to remain alkaline. An attempt should be made to keep the urine output between 1000 and 1500 cc. daily, but in cases with marked oliguria or anuria care should be taken not to overload the patient with sodium salts.

Sodium Lactate.—Fox (1944) took a position somewhat opposed to the use of plasma, and in 1947 said that the large amount of data that had now accumulated indicated to him that survival of severely burned patients is dependent upon the volume of sodium solution administered and not upon the presence of protein; patients treated with plasma or blood invariably died in his experience unless the total volume of sodium-containing fluids given was from 10 to 15 liters (given in 1 75 per cent sodium lactate solution by mouth at 15-minute intervals) for a 70-kg. adult He said he had found no evidence that blood [illegible]

tained much potassium; on the other hand, when apparently excessive therapy was given to less severely burned patients they excreted large volumes of urine containing considerable sodium. Fox also said it seemed to him that sodium deficiency is a large factor in accounting for the death of patients from the tenth to the thirtieth day after injury—*after* the shock phase is passed—for the plasma and urine sodium of these patients become very low. He found correction of late sodium deficiency to be quite difficult and usually not successful, but its prevention was accomplished by giving at least 10 gm. of sodium bicarbonate and 10 gm of sodium chloride daily from about the fourth to the twentieth day after injury.

Lund *et al.* (1946), commenting upon this work of Fox, said it appeared to them that sodium salts are necessary adjuncts to the treatment of burn shock but not the sole therapeutic agents, they stressed the fact that in Fox's studies the sodium is chiefly used as prophylaxis and not for treatment of fully developed shock, and that dangerously low plasma protein levels were seen in some of his patients It is hoped that further experience will reconcile the two viewpoints.

Asphyxiation and Respiratory Tract Injury.—In some instances anoxia will be the result of carbon monoxide poisoning but usually it results from pulmonary injury consequent upon the inhalation of flame, smoke, or superheated air Of course the administration of oxygen is obviously called for, but many of these patients may be rendered so maniacal by their suffering that they cannot easily be sufficiently quieted to make the administration of oxygen feasible, and oftentimes in addition the administration of oxygen to patients who have burns about the face and the naso-pharyngeal mucosae is extremely difficult. It seemed that most of the victims of the Cocoanut Grove disaster with irritated inflammatory lesions of the upper respiratory tract treated at the Boston City Hospital had some favorable effect from the use of expectorants, but only after twelve to twenty-four hours or longer, and it was not held

citrate and enjoin great caution in the further use of plasma, though admittedly the citrate reactions have occurred very rarely.

Lund *et al.* (1946) said that serum may be used in place of plasma with equally good results; reactions no longer follow its employment, probably because of the disappearance of the toxic substances in the two weeks it is held nowadays before use.

Human serum albumin also rarely gives rise to a reaction nowadays and may be satisfactorily used as a plasma substitute; however, its cost is so high that it is not likely to enjoy much popularity in civilian practice.

TABLE 25.—PLASMA AND ELECTROLYTE DOSAGE IN BURNS (MODIFIED FROM LEVENSON ET AL.)

First Dose of Electrolyte and Plasma According to the Weight of the Patient

Weight	10% Dextrose Electrolyte in Saline Solution	Plasma
lb.	cc.	cc.
150 or more	1500	750
100–149	1000	500
50– 99	500	250
35– 49	250	250
20– 34	150	150
5– 19	5 per lb.	10 per lb.

Subsequent Amounts of Electrolyte and Plasma to be Given for Each Point Rise in Hemoglobin or for Each Point it is Above 100 Per cent According to the Weight of the Patient

Weight	10% Dextrose Electrolyte in Distilled Water	Plasma
lb.	cc.	cc
150 or more	50	50
100–149	35	35
50– 99	20	20
35– 49	15	15
20– 34	10	10
5– 19	0 5 per lb	0 5 per lb

It should be noted that in making the hemoglobin determination venous rather than capillary blood must be used because of stagnation in the capillaries, furthermore, if whole blood is being given instead of plasma the hemoglobin value will not be a reliable indicator of blood volume

It seems to me unlikely that bovine albumin, isinglas, pectin or even gelatin will soon be employed to any extent outside experimental clinics as a substitute for plasma.

Alkalinization of the Urine.—Reversible azotemia, oliguria and even anuria occur frequently in burns of moderate to great severity and reflect either the [illegible] or more probably [illegible] by heat injury to [illegible] of alkalini-

may also be given At least, then, there seems to be no doubt about the advisability of using penicillin in severely burned individuals

Toxemia.—Nowadays when shock is so vigorously attacked patients are beginning to die at a later period, *i e*, surviving the shock but apparently dying from toxemia. Lund *et al.* (1946), in their excellent review of the subject of burns, said there seems no doubt that many chemicals are released from the area of a burn that all together play a part in the depression of the circulatory system, and they pointed out that though the literature concerning the toxic factor or factors in burn shock is voluminous and very controversial, few authors have been positive in their denial of such a possible contributing factor. Apparently, according to the studies of Walker *et al.* (1946), this burn toxemia is a wide-spread process involving many if not all of the organs and tissues. No specific treatment is as yet known, but it would seem from the work of Van Duyn (1945) that possibly the giving of large whole blood transfusions, begun immediately after the period of hemoconcentration and repeated as indicated by the appearance and disappearance of degenerative changes in the white cells, is the best general measure available to combat toxemia

Anemia.—The cause of the progressive anemia in severe burns is not well understood. It will respond only to blood transfusions, large dosage with iron, liver extract, proteins or vitamins will not overcome it. Levenson *et al* (1946) advocated the giving of whole blood or red blood cell transfusions in sufficient amounts to keep the hemoglobin at 90 per cent.

Hyperpyrexia.—Levenson *et al.* (1946) said that the patient with a burn does not tolerate a high temperature and will die if it remains at or above 105° F. (40.5° C.) for a few hours; therefore measures must be directed toward [illegible]

patient's bed if necessary to help to bring the temperature down

Nutrition.—Burned individuals frequently lose a great deal of protein through necrosis and exudation, and if they have a long siege of grafting operations they often lose their appetites Such patients may become seriously edematous as a result of the low plasma protein level Leonard (1946) said that in the treatment of victims of the Hartford circus disaster at the Hartford Hospital, amigen in 10 per cent solution with or without dextri-maltose was masked in soups and broths and disguised in tomato juice, cherry juice, strawberry juice, grape juice and even in ginger ale. In this way from 25 to 100 gm , or even 200 gm , of additional protein could be added to the patient's diet so that the total protein intake was increased to from 125 to 300 gm. a day in almost every case. It was necessary to time the giving of the amigen carefully, for if it was given too closely before meals or in too great an amount with meals the regular diet was often refused or poorly taken. For patients [illegible]

1300 cc of a solution composed of 4 per cent hydrolysate and 15 per cent dextrose, or 50 gm. protein and 1000 calories. Levenson *et al.* (1946) said this quantity can be given into a large vein with a 20- or 21-gauge needle in four hours without much danger of thrombosis to the vein, and that it can be

certain that the improvement would not have taken place without the aid of these drugs. The use of compound tincture of benzoin in the usual manner with steam from a kettle of water seemed usually to contribute to improvement and comfort when it was started during the second or third day after the employment of the more strictly emergency measures had been completed. However, Finland *et al.* said that perhaps the most useful procedures that

rates and other sedatives were also of great benefit in these cases.

Eighteen tracheotomies were done at Boston City Hospital upon Cocoanut Grove victims; three of these patients lived, but it was felt that possibly some ... had been performed at ... e suction together with ... were indicated.

... tion of the burned area are later described in the section on the local treatment of burns, but despite the utmost precautions it is probably well to assume that all burns are contaminated and may become infected. On the basis of his experience in the Cocoanut Grove fire, Cope (1944) stated that the use of sulfonamides either *by mouth or intravenously is indicated for all burned patients except those* ... intact ... ll not ... of the sulfonamides in the treatment of the burn cases at the Boston City Hospital after this same fire but that it was felt on the whole the employment of these agents was responsible at least in part for minimizing pulmonary infection and for preventing delayed deaths from pneumonia in many cases. Leonard (1946) said that at the Hartford Hospital each victim as he entered during the Hartford circus disaster was given, immediately after determination of his hemat ... 15 to 30 grains (I ... pound (0.5 kg.) ... y four to six hours for the adults and a comparably smaller dose for the children However, *since the catastrophe coincided* with a period of excessively hot and humid weather tending to accentuate the oliguria of shock and precipitate a serious situation, many patients showed red blood cells in their first specimens of urine, while in a few gross hematuria developed. The use of sulfonamides was therefore discontinued within twenty-four to forty-eight hours in all cases, and it was the conclusion as a result of this experience that sulfonamide drugs are dangerous and definitely contraindicated in the initial treatment of burns Upon special appeal (the agent was not at that time freely available) penicillin was obtained and was thereafter given to all severely burned patients intramuscularly. It was concluded that several patients would have died of sepsis had it not been for the liberal use of penicillin paren- ... the rarity of invasion of the blood ... mic constantly used and ... in attendance. Levenson ... ould be started on entry ... ulfadiazine in full doses

pressure bandages for burns of the face, head and neck and the regions of the genitalia and anus. Levenson *et al.* said that these regions should be merely covered with a thick layer of sterile petrolatum and one layer of fine mesh gauze and nothing else; Lund *et al.* (1946) were also of this opinion and advocated the application of the dressings in rectangular strips that can be replaced at intervals as they are rubbed off.

Colebrook *et al* (1947), in England, used a sulfathiazole-penicillin cream under their compression bandages; local antiseptic measures of this sort do not enjoy favor in this country, though some men do prefer petrolatum gauze to dry gauze.

The initial dressing is left in place for about fourteen days, at the end of which time superficial second degree burns are healed and deep burns are beginning to slough. When a new dressing is put on, operating room conditions must again prevail.

layers of sterile open mesh gauze, fitted carefully without overlapping and, in burns of the hand, surrounding the thumb but not going between the fingers. Very thin plaster slabs are then moistened and molded over the extremity front and back, a thin layer of rolled plaster then completes a nearly skin-tight, light, well-fitting plaster which extends three to four inches above the burn; the fingers are placed in a semiflexed position.

Lund *et al* (1946) said that the application of plaster-of-Paris casts is suitable for burns of the extremities, particularly for burns of the hands, but is not recommended for burns of the trunk, buttocks or head. The cast must extend distally to cover completely the hand and foot, including the tips of the fingers and toes, even if these areas are not burned; otherwise circulation will be seriously impaired. Hands should be put up in the position of function with a slight cock-up at the wrist and the fingers in neutral position. An objection urged against the plaster cast is that the degree of immobilization of joints it provides is not desirable. However, Colebrook *et al* (1946), in England found a cast the only answer to the exploring fingers possessed by so many children; but they had in mind only a thin shell of plaster-of-Paris over the compression bandage.

The original cast is left in place for fourteen days and if the burn has not healed at the time of its removal another is applied at once and left on for a further period of fourteen days.

Skin Grafting.—This matter is entirely outside the province of this book, but for a fine review of the subject the reader is referred to the paper of Lund *et al.* (1946).

LOCAL TREATMENT OF MINOR BURNS

As stated above, experience in industrial practice has shown that the average minor burn is best treated by a small compression bandage. For even more

repeated three times a day; administration at a faster rate is limited by the fact that nausea, glycosuria and excessive diuresis, and thrombosis may be caused. Levenson *et al.* also said that in the late stages of severe burns testosterone propionate should be given in doses of 25 mg. intramuscularly every other day to increase the positive nitrogen balance by reducing the loss of nitrogen in the urine.

Tetanus Prophylaxis.—It is routine practice in many hospitals to give to the burned patient whose epidermis is broken a prophylactic dose of tetanus antitoxin or a booster dose of tetanus toxoid if he has been previously immunized.

LOCAL TREATMENT OF MAJOR BURNS

Cleansing and Débridement.—In this country we are now fully committed against initial cleansing and débridement. The maneuvers are often exquisitely painful and indeed may require the administration of a general anesthetic in order to permit their accomplishment, and they tend to aggravate shock. Furthermore, it has not been established that unopened blebs become infected, or that the dirty undébrided open wound surface is any less likely to become

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treatment of severe burns of Levenson *et al.* (1946), it is directed that blisters must not be cut or broken and no attempt be made to wash or clean off any dirt of any kind; in our Army since 1945 it has been forbidden to apply anything to a burned surface except sterile petrolatum gauze or sterile fine mesh dry gauze.

Compression Bandage.—There is practically universal testimony both in the Armed Forces and in civilian practice to the superiority of the compression bandage type of treatment to any that has heretofore been used in extensive burns. Indeed, McClure and Lam's (1943) statistical study of minor industrial burns found the method superior to all others even for individuals who remained ambulatory. The technic of pressure dressing described by Levenson *et al* (1946) consists in applying, under operating room conditions, *fine mesh gauze, dry, directly to the wound surface*; over this sufficient Surgine (a composite cotton dressing material used in many hospitals for abdominal pads) should be wrapped to make possible even compression by means of ... the aim being that the *final dressing after compression*

patient because the greatest amount of swelling occurs in the ...
following injury. Since the swelling occurs in the immediately adjacent as well as in the burned areas, these must also be incorporated in the dressing. In burns ... must extend distally to cover *completely the*

dressings may have to be removed because of ...
of an extremity with a properly applied dressing often helps prevent stasis and discomfort. In applying a pressure dressing the tension must be uniform and care must be taken that no more pressure is used than required. Where

Chromic acid burns require special treatment because this agent does not hydrolyze within the tissues and its action may persist for many days: after initial lavage, apply wet dressings of 5 per cent ammonium polysulfide for three days, followed by wet dressings of 5 to 10 per cent sodium citrate, sodium lactate, or sodium potassium tartrate for the purpose of stripping the chromium from the tissues, the latter dressing to be continued for a period of three to five days also.

In their experimental studies Keating and Travell (1943) found that 95 per cent alcohol was by far the most effective agent for removing phenol (carbolic acid) from the skin.

[illegible]

any obvious particles of phosphorus disclosed by examination *in the dark*

[illegible]

bicarbonate of soda solution for a long period—*i. e.*, small burns one-half hour, large burns one to two hours—or if immersion is impossible keep it covered with sterile dressings repeatedly wetted with the bicarbonate solution; (4) finally, do not dress as for an ordinary burn until reexamination in the dark has revealed complete lack of phosphorescence.

In our Army toward the close of War II there was issued a copper sulfate pad to be personally applied by the soldier after he had immediately poured water over the burned site

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SHOCK

PRIMARY SHOCK

(*Immediate or Neurogenic Shock, Vasovagal Syndrome*)

[illegible]

he becomes warm and reassured. However, there is a very definite type of "primary" shock in which the patient may complain at first of being warm and nauseated but soon becomes cold and clammy with extreme pallor, a slow feeble pulse, and a blood pressure so low that it may not be measurable. The patient usually faints. This type of shock may result from the severe

minor "household" burns, Aylwin-Gibson (1943) stated that she had learned through many years' experience that malt vinegar quickly and lavishly applied is the most effective of all agents both for relieving pain and preventing blistering. Levine (1943) found hexene-ol, a fatty alcohol discovered in the development of synthetic rubber, very satisfactory in a series of 238 minor burns; the agent effected prompt and lasting relief from pain, prevented the formation of blisters, and itself caused local irritation in less than 1 per cent of the cases in the series; it did however produce localized perspiration and Levine therefore felt that it was not advisable to treat extensive burns with it since the promotion of much body fluid loss might thus be brought about

BURNS OF THE EYE

Patients treated at the Massachusetts General Hospital after the Cocoanut Grove fire had 5 per cent sulfathiazole and petrolatum placed in the burned eyes, the lids closed, and the eyes incorporated in the pressure dressing of the face, only the nostrils and mouth being left uncovered.

Jacoby (1942) said he had used the following treatment successfully in several hundred cases of shipyard workers who had sustained "flash" ultraviolet burns of the eye: instill one or two drops of 1 per cent pontocaine into each eye and have the patient sit before an infra-red lamp at a distance of approximately 18 inches and gaze steadily at the lamp for a period of twenty minutes.

For the treatment of chemical burns see below.

CHEMICAL BURNS

I believe it is the consensus that in cases of acid or alkali burns the heat of chemical reaction from neutralizing agents more often than not may add injury to that already produced by the caustic agent, and that therefore the best results are to be expected when the agent is flushed away through the copious use of water. However, the temptation to effect neutralization is so [illegible] sodium [illegible]

induced may be so great that anesthesia should be instituted first. [illegible] and Haas (1943) proposed a phosphate buffer solution for the neutralization of both acid and alkali burns: 70 gm. of monobasic potassium phosphate and 180 gm. of dibasic sodium phosphate are dissolved in 850 cc. of water The advantage claimed for this phosphate buffer solution is that it will effect prompt neutralization of the offending chemical without introducing the new complication of an alteration in the pH of the tissues, application to the normal eye was said merely to result in some conjunctival hyperemia that disappeared on the following day. Terry (1943) wrote that he had practically elim- [illegible] plant through [illegible]

there is such delay that destruction of the epidermis has [illegible] the part drenched with the ammonium chloride solution for ten or fifteen minutes and then with plain water or normal saline for one hour continuously, thereafter treating as for a heat burn. The eyes are irrigated for five minutes with the ammonium chloride solution and then for the rest of the hour with boric acid-saline solution.

the fact that in some instances a state of sublethal shock continues for several days and that finally renal deficiency often dominates the clinical picture, *i.e.*, that this condition may obtain not only in the crush syndrome (*q.v.*) but in ordinary secondary shock as well.

The most important point with regard to secondary shock is that when the patient has sustained injuries sufficiently serious so that shock may be expected he must be treated at once, for to wait for a profound fall in blood pressure before instituting therapy may be to allow the patient to go into the state of "irreversible" shock from which no amount of treatment will retrieve him.

Therapy

Control of Hemorrhage, Wounds and Fractures.—A few years ago, McMichael (1942) stressed the point, as a result of experience in the air raids in England, that the patient should be undressed as quickly as possible in order to make a full assessment of the extent of the injuries Further blood loss should [illegible]

the tissues beyond it. If, however, a tourniquet must be used it should be applied tightly enough to occlude both the arterial and the venous flows and it must be removed for a short interval at least every hour The application of cold compresses or actual ice packs to the limb beyond the tourniquet may prolong the viability of the tissues It is especially important to remember that when the tourniquet is removed permanently the return of the circulation to a badly damaged limb may result in a serious loss of plasma that can be prevented by the application of a compression dressing before the removal of the tourniquet When the limb is so hopelessly damaged as to demand early *amputation, the tourniquet should be left in place until the operation has been* performed in order to prevent the loss of both blood and plasma. Extensive wound toilet should not be attempted as a first-aid measure; but if the wound is a penetrating one in the chest wall, it is imperative that the skin over it be closed by any means at hand. The urgent necessity to prevent any further damage to the soft tissues and the blood vessels makes it mandatory to attempt immobilization of fractures at the earliest possible moment, preferably before the casualty is moved from the scene of the accident.

Relief of Pain.—The relief of pain with morphine has been since time out of mind one of the primary principles in the treatment of traumatic shock, but it seems to me that there is nowadays rather good reason to question the [illegible] ripheral circulation is [illegible] receives any benefit [illegible] ideed, Beecher (1944) reported that during War II morphine poisoning was encountered not infrequently in casualties who had been given several successive subcutaneous injections of morphine in the forward areas and then absorbed it all at a later time when they responded to the other measures directed toward the control of shock. Beecher advocated the administration of morphine intravenously in shock, or where that is not possible its deep intramuscular injection followed by massage, the site of the injection being made low enough on an extremity so that if signs of poisoning subsequently develop a tourniquet can be placed above the morphine deposit in order to slow down the absorption rate. Then too, it is actually a fact that the patient in shock does not usually

acute pain of sudden trauma or the dressing of a wound, or even in rare instances from the prolonged intolerable pain of renal or biliary colic, from the excessive manipulation of viscera at operation, or even from a severe emotional strain.

THERAPY

The experiments of Phemister *et al.* (1944) indicated that hemoconcentration does not occur in primary shock, and it is universal experience that these patients recover in an hour or so if they are put at rest in a recumbent position, kept warm and given a sufficient dose of an analgesic to control their pain. However, the patient must be continually watched because he may after a time go into true "secondary" shock, and therefore if there has been much loss of blood or if the tissues have been considerably traumatized, it is probably good routine practice to attempt to forestall secondary shock by instituting treatment for it at once (see below).

SECONDARY SHOCK

(Delayed, Traumatic, or Oligemic Shock)

This is the type of shock that occurs insidiously an hour or more after a patient has received a severe injury. As a result of massive hemorrhage either externally or into the tissues, or of the considerable loss of plasma externally in the burned patient or through extravasation into the tissues in the severely traumatized one, there is reduction in circulating blood volume, reduced

hemoconcentration is recorded, particularly in severe burns and in instances in which there has been a great deal of plasma extravasation into the tissues or of serous or seropurulent exudate into a cavity. In the beginning the patient becomes restless and very thirsty and breaks out into a cold, clammy perspiration. As the state progresses he becomes increasingly weak and cold and pallid and the lips, ear-lobes and finger tips may become grossly cyanosed. One of the most valuable diagnostic signs is a subnormal temperature, though of course at times complications may prevent this, as in the acute infections, in which shock may supervene as the result of an uncompensated increase in the size of the vascular bed. For a considerable period the blood pressure may remain nearly normal as a result of compensatory arteriolar constriction in the skin and splanchnic areas, but the pulse is usually small, weak and rapid. Cope (1944) said that some cases had been reported among the air raid casualties in England in which the pulse rate remained slow; he called attention to the fact that most of these patients were over fifty years of age; for the rate

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mounting acidosis, or a hypothetical toxin formed in the tissues—but the result is a progressive and persistent fall in blood pressure and death if the ... combated before the fall has become very great. In some

remain approximately normal nearly to

n will be indicated by a high diastolic

ing man whose systolic pressure was 135

Moon (1947) has recently reemphasized

that there has not occurred generalized fluid loss through abnormally permeable capillary endothelium but rather total blood loss through ruptured vessels This fact of course makes it essential to administer whole blood in such cases; nowadays it has become customary to use plasma only as a sus- [illegible]

injury it was usual to find from 1000 to 1500 cc. of blood in the abdominal cavity; bilateral amputations would usually require 1000 to 2000 cc. He said that it was sometimes necessary to give as high as 5000 cc before operation, but that unless there was continued bleeding this was very unusual. One of Birchall's (1946) patients, who had an abdominal wound with laceration of the inferior vena cava, was given 7500 cc of whole blood preoperatively and during the operation; after ligation of the inferior vena cava the hemorrhage ceased and the patient made a good recovery.

Oxygen.—In instances in which there is embarrassment of respiration due to traumatization of some portion of the respiratory apparatus, the administration of oxygen in high concentration is of course indicated. A great deal of study has been devoted to the question of oxygen administration in shock *per se*, both of hemorrhagic and traumatic origin, but I shall not review the literature here since it does not show definitively that oxygen administration has a secure place in the therapy of these types of shock.

Jacobi *et al.* (1946) showed that gaseous oxygen intravenously administered at pressures at or slightly above venous pressure, and at rates of 60 to 600 cc. per hour depending on the size and age of the patient, can be given with safety. They felt that oxygen administered in this way may be efficacious when its *inhalation* fails to yield therapeutic effects, for by the intravenous route a lung rendered functionally deficient through edema or some other mechanism can be by-passed and the necessary oxygen made available to the body. This is a very interesting observation, but it is necessary to call attention to the fact that their number of cases was very small and that much further work will be needed before one can be certain of the validity of this viewpoint.

Drug Therapy.—It would be a mighty fine thing if we had a drug with which to combat shock, and the current researches whose aim is the production of such an agent are certainly worthy of support, but as yet no satisfactory drug has been made available Certainly all of the vasoconstricting agents are contraindicated because in shock there already exists a maximal reflex arteriolar contraction, epinephrine especially is not to be employed for the reason that its primary arteriolar constrictor action is succeeded by a prolonged generalized capillary dilatation. Ephedrine, benzedrine (amphetamine), metrazol, coramine (nikethamide), caffeine-sodium-benzoate, strychnine, and all the other analeptic agents have had their advocates, but none has stood the test of time. During War II, Russian workers (Stern, 1942) claimed that the intracisternal injection of potassium phosphate proved its worth in the treatment of shock in the field, but a lot of evidence will have to be forthcoming to substantiate this claim.

CEREBRAL SHOCK

Sometimes in cases of severe head injury the circulatory disturbances will be neurogenic in origin in that they result from injury to the centers of cardio-

complain of pain, and therefore except for its quieting effect there would seem to be no reason for giving the drug; a quick-acting barbiturate, such as seconal or amytal, might often be effectively substituted, I should think. McMichael (1944) stated that during the blitz in England it was often observed that patients became restless and began to complain of pain only as the blood pressure was recovering; he felt that then was the time to give morphine, if necessary intravenously by injecting it into the infusion tubing. If there is severe head injury certainly the barbiturates only should be used for under these circumstances it is common knowledge that morphine greatly aggravates the state of anoxia, Gurdjian *et al.* (1939) made the further point that in these cases morphine produces a tremendous rise in cerebrospinal fluid pressure that may endanger the life of the patient.

Body Temperature.—The patient in shock both looks cold and feels cold

and rosy in appearance; but it seems that everybody has been neglecting to determine whether we were not hastening his exitus in this way. The animal experiments of Blalock and Mason (1941), confirmed by those of Wakim and Gatch (1943), showed that significant elevations of temperature shorten the period of survival, a finding not surprising in view of the fact that the cooler the tissues the lower their oxygen requirement. But it does not follow that the deliberate application of cold to the body of the shocked patient is therefore necessarily indicated, nor at the time of writing have I seen any report of a controlled series of cases in which the worth of such a procedure has been shown. The opinion of qualified clinical observers now seems to be, as I gather it from the writings of Cope (1944), and McMichael (1944), both summarizing extensive experience during War II in England, from the Harvey Lecture of Richards (1944), summarizing the studies of shock at Bellevue Hospital, from the memorandum on shock of the National Research Council of Canada (1943), and from our own National Research Council Military Manual on Shock and related conditions (1943), that sufficient covering should be applied to prevent great loss of body heat, but that the excessive and continued application of external heat should be avoided for three reasons. first, because warming of the skin will draw considerable blood away from the already depleted circulation of the vital organs; second, because the utilization of oxygen will thus be greatly increased; and third, because the patient may be caused to perspire which would only lead to a further depletion of his body fluid.

Position of the Body.—It is generally accepted that the head-low position, achieved by raising the foot of the bed 10 or 12 inches, is beneficial to the shocked patient, but one should remember the important exception, namely, that the patient with a head injury should have his head slightly elevated because when it is lowered there is likely to be an increase in hemorrhage both from the scalp wound and into the brain. Furthermore, rapid changes of position should not be made in any case; they may cause sudden death, just why is not known.

Restoration of Blood Volume.—There is now complete realization of the fact that, with the exception of burn cases (see Burns), most surgical shock seen in war casualties and in serious civilian casualties is due to the rapid loss of whole blood; the fact that hemoconcentration is usually not great indicates

CRUSH SYNDROME

This is an entity of which we have been made aware principally through the observations of the British during the blitz in War II. The patient is one in whom compression of muscle masses by heavy objects has been maintained for some time; after he is extricated from the wreckage and the compression is released he is likely to go into secondary shock in a few hours, and then in a matter of hours to days—oftentimes after the shock has responded well to therapeutic measures—evidences appear of progressive damage to the renal tubules. The true cause of this renal injury has not yet been determined but it is thought either to be due to some toxic product of damaged muscle tissue or to result from generalized intravascular hemolysis or to follow upon prolonged ischemia of the kidneys themselves. In fatal cases anuria develops and the patient is carried off in uremia usually toward the end of the first week after the injury was sustained. It seems that the extent rather than the duration of the concussion is of the greater importance in prognosis.

THERAPY

In the event that the patient is seen very early, at or shortly following his release from the wreckage, pressure bandages should be applied to the parts involved and they should be only slowly released in order to prevent a sudden flooding of the circulation with the hypothetical toxic products from tissue necrosis; the application of such pressure bandages will of course also prevent rapid extravasation of plasma into the damaged tissues and thus limit the degree of secondary shock. Plasma must of course be given (plasma administration is discussed in Burns) and fluids also by mouth and parenterally in the attempt to maintain a satisfactory urinary output. In the very complete discussion of the crush syndrome in publication 2212 of the Office of Civilian Defense (May, 1943), it was stated that 5 per cent dextrose solution is preferable for parenteral administration to saline solution because of the latter's edema-producing properties and its possible harmful effects on the damaged kidneys. The administration of alkalis to prevent the precipitation of myohemoglobin in the renal tubules has not been strikingly effective, the use of mercurial diuretics is absolutely contraindicated. Amputation of the involved extremity, decapsulation of the kidneys, multiple incisions into the tense, edematous, traumatized muscle masses, the administration of adrenal cortical substance and of atropine and papaverine, have all been tried but without consistently good results.

BLAST SYNDROME

This entity was seen a great deal during War II, especially during the blitz in England, but is unlikely to be observed often in peace time. Whether due to air or water (immersion) blast, this syndrome is associated with severe shock, often with injury to the central nervous system and the intra-abdominal viscera, and universally with lung damage. The predominant pulmonary lesions are bilateral and are due to hemorrhage and capillary bleeding following alveolar damage and rupture as a result of the impingement of a blast of air or water upon the body wall, pressure changes in the lungs transmitted through the trachea playing no part in the production of the lung lesions. Blast injury

vascular control in the medulla—the blood pressure falls, the pulse becomes very slow oftentimes, and there may be deep, stertorous, or periodic breathing. In these cases the type of therapy employed in secondary shock not only fails to be beneficial but frequently aggravates the patient's condition because both the head-low position and transfusion tend to increase intracranial bleeding. I do not know what there is further to say about these cases except that the ministrations of a skilled, quick-working surgeon offer about the only hope that there is for such patients.

SURGICAL SHOCK

The shock that not infrequently occurs during a surgical operation differs from ordinary secondary shock in that in addition to the local loss of blood there is the insult of the anesthetic, the often prolonged emotional disturbance that preceded the operation, and the possible absorption of the toxic productions of infection or autolysis. We do not have any magical procedures, however, to combat all of these things, and the treatment of this type of shock must therefore in the present state of our knowledge remain that of secondary shock. Not infrequently recovery is spontaneous following the cessation of manipulation or of the administration of the anesthetic. There is some evidence that animals with a low vitamin C level are more susceptible to shock than normal animals, and since the vitamin C level is said to diminish in the human after the performance of major surgical procedures, the suggestion has been made that the preoperative intravenous administration of vitamin C might be of value in preventing shock; I have seen no definitive clinical study in support of this suggestion.

CARDIOGENIC SHOCK

This is the type of shock resulting from sudden diminution of cardiac output in myocardial infarction. There is neither decreased filling of the left ventricle nor loss of circulating blood volume, and therefore the measures employed to combat secondary shock are not indicated here. This type of shock is more appropriately dealt with in Coronary Occlusion.

ANAPHYLACTIC SHOCK

In the literature of recent years there have been a number of reports of animal experiments in which there was recorded decreased blood volume and increased blood concentration in anaphylactic shock, these phenomena apparently resulting from a sudden wide increase in the size of the vascular bed consequent upon increased capillary permeability. In man, Black and Kemp (1937) observed an increase in the specific gravity of the blood during an acute reaction to ragweed pollen, and Meyler (1939) reported hemoconcentration in two cases of extensive serum disease in man. Blotner (1942) recorded the case of a patient in severe anaphylactic shock following the administration of tetanus antitoxin whose symptoms so closely resembled those of secondary [illegible] was

[illegible]

These two case reports of course prove nothing, but they certainly [illegible] the interesting speculation that possibly plasma therapy might prove to be of specific value in the treatment of the oftentimes alarming anaphylactic shock. Plasma administration is discussed in Burns.

TOXIC AND OTHER SPECIAL FEATURES OF SULFONAMIDE THERAPY

[illegible]

recognized types of reaction there may be revealed at autopsy necrotizing fibrinoid arteritis of the smaller vessels in the lungs, lymph nodes, spleen, adrenal [illegible]
Schaffer [illegible]
that in [illegible]

thelial cells in the affected area. Furthermore, it is now known that a true toxic nephrosis is sometimes caused by these drugs as well as the more familiar type of disturbance resulting from precipitation of the relatively insoluble acetylated form of the sulfonamides. In brief summary then, one must say that although the sulfonamides are unquestionably among the most valuable agents ever introduced into therapy they are nevertheless indubitably toxic and potentially dangerous drugs and should for that reason be administered with due respect for their harmful potentialities.

Occurrence of Reactions on Full Therapeutic Dosage.—Since sulfadiazine is employed for systemic sulfonamide action very much more than any of the other compounds, principally for the reason that in addition to being highly efficacious it is almost certainly the least toxic, I shall present here principally the evidence of what to expect in the way of toxicity from this agent.

Plummer and Wheeler (1944) recorded the reactions to sulfadiazine in 1357 patients, principally adults. In this series, sixty-three patients (4.6 per cent) experienced a renal reaction, in all but five instances unaccompanied by fever or rash; twenty-two (1.8 per cent) had a drug rash, accompanied in nineteen cases by fever; fifteen (1.1 per cent) developed leukopenia with or without granulocytopenia; of the remaining twenty-one reactions, four were drug fever alone, nine were nausea and vomiting, one was thrombocytopenic purpura (this was a fatal reaction), two were instances of jaundice, one of conjunctivitis, one of stomatitis, one of headache and vertigo, one of encephalopathy and one of arthralgia.

In a study of approximately 5000 infants and children receiving sulfonamides during a period of two and a half years, Fink and Smith (1946) reported a total incidence of important complications of less than 1.4 per cent. Most of the patients received sulfadiazine though in the beginning some received sulfathiazole and during one six-month period sulfamerazine was used exclusively. The usual dosage of sulfadiazine and sulfathiazole was ½ grain (30 mg.) per pound body weight as an initial dose, and a maintenance dosage of 1 grain (60 mg.) per pound per twenty-four hours, divided into four or six equal

is sustained only by individuals who are within a few feet of the explosion and therefore in almost all instances the patient is suffering not only from blast but from severe injuries of the usual traumatic nature, so that the picture is *nearly always a very complex one* Recovery from blast injury, when it occurs, is said to be apparently complete; Tunbridge (1945) listed deafness and post-concussive syndromes as the only sequelae.

Of course there is another type of blast injury as the result of the transmission of the force of an explosion to the body through a solid structure, such as when the detonation of a high explosive in the proximity of a semi-rigid body such as a ship or a tank results in the transmission of energy through the solid structure as a flexion wave resulting in the sudden acceleration of the deck or of bulkhead surfaces. Since this type of injury is caused by a sudden acceleration, the damage is greatest at the point of contact and the injuries are usually to the lower extremities, particularly the ankles, or to the pelvis if the individual is seated on the accelerated structure. Obviously, the type of injury inflicted does not come within the description that I have given here, the primary lesions being predominantly skeletal and vascular and affecting chiefly the lower extremities

It seems also that the term "cerebral blast syndrome" has come to be applied by psychiatrists during War II to the entity recognized during and subsequent to War I as shell-shock. These cases are apparently a reflection of extreme hysterical anxiety states, and thus obviously differ entirely from the two types of physical blast syndrome above presented.

THERAPY

[illegible] blast syndrome [illegible] 943), the thera- [illegible] e shock and the [illegible] rgent attention.

In the severe case with rapidly developing pulmonary edema venesection may be necessary as a life-saving measure, but since this is just the wrong thing to do for shock one must thereafter as soon as possible *administer plasma* intravenously In some instances it seems that oxygen under positive pressure controls pulmonary edema without the resort to venesection. Since these *injured lungs* are extremely susceptible to the development of secondary pulmonary infection, the prophylactic administration of penicillin might be advisable in selected cases

the patient had had no reaction after nine days of therapy his chances of developing one subsequently on the same administration diminished rapidly.

Effect of Route of Administration on Toxicity.—Of the 244 patients of Plummer and Wheeler (1944) who were given one or more intravenous injections of sulfadiazine, 12.3 per cent had some form of reaction as compared with 8.9 per cent of reactions in 912 patients treated orally with 6 gm. daily. The difference in the number of renal reactions in the two groups was more striking; in those given intravenous injections renal reactions occurred in 7.4 per cent, whereas in those treated orally such reactions occurred in only 4.5 per cent. There were two cases of mild and transitory jaundice with possible toxic

knowledge that one is probably considerably increasing the likelihood of the occurrence of serious reactions.

Sensitization Through Local Application.—The local cutaneous application of sulfonamides, particularly sulfathiazole, gives rise in a not inconsiderable proportion of cases when administration is continued for more than a week to a contact type of dermatitis, with or without a disseminate eruption, or a local or generalized exacerbation of the skin disease for which the drug is being used. In some of these cases the local sensitization thus induced persists so that when the drug is taken internally at a later time there will be a return of the local signs of sensitization. I have not seen any record of the occurrence of visceral lesions as a result of this cutaneous sensitization, but that is no reason to minimize the seriousness of this occurrence since the skin reactions as a result of sensitization may be very severe indeed and force the discontinuance of sulfonamide therapy when it is direly needed for the treatment of a serious systemic infection. Furthermore, some of these skin reactions have themselves resulted fatally. The studies of Shaffer *et al.* (1943) and others showed that in some instances the sensitizing application of the drug may not produce local dermatitis and can only be shown retrospectively to have sensitized the patient when he is seen to respond very quickly and in a violent fashion to subsequent administration either locally or orally.

Sensitization Through Systemic Administration.—When an individual has received a sulfonamide for a week or more by mouth or parenterally and has developed a reaction of some sort, he is extremely likely to develop the same

be "serious" but the important point is that seven of the nine occurred in patients who had previously experienced sulfonamide reactions. It is, however, not clearly established that a first course in which the patient develops no reaction may nevertheless sensitize him so that he will develop reactions upon subsequent administration. Indeed, the report of Siegel (1944) probably indicated with fair certainty that *short courses* of sulfadiazine may be frequently

doses. The maintenance dosage of sulfamerazine was from ½ to ¾ grain (30 to 45 mg.) per pound per day. It was noted in this study that the sulfonamides may produce or aggravate gastro-intestinal and neurologic disturbances in acutely ill children, such reactions being rarely noted in children receiving the drugs during convalescence or at a time when they were well. Renal complications apparently occurred much less frequently in these children than in adults, though two deaths from anuria not associated with crystalluria occurred in the series. Untoward effects on the hematopoietic system were also uncommon in the children and when present were usually associated with evidences of a general reaction such as fever and rash.

Occurrence of Reactions on Prophylactic Dosage.—Coburn (1944) reported that in the group of 30,000 Navy personnel to whom 15 grains (1 gm.) of sulfadiazine were administered daily during three months, evanescent rashes occurred in 0.5 per cent of the individuals and dangerous constitutional disturbances in only 0.01 per cent There was only one death in the series, that of a man to whom therapeutic doses of sulfonamides were given while he had a sulfonamide rash and bronchitis induced by the prophylactic employment of the drug.

Lethality of the Toxic Reactions.—Plummer and Wheeler (1944) reported that at the New York Hospital only one death had occurred in 2853 patients given sulfadiazine in full therapeutic dosage. This is certainly a low rate, though there are other drugs ordinarily looked upon as rather toxic that have a rate somewhat lower than this. For example, Grollman and Slaughter (1947) estimated that chloroform has a death rate of about one in 4000 inhalations. So the reader will do well to bear in mind that when he administers sulfadiazine to a hospitalized patient under ideal circumstances he is nevertheless subjecting him to a risk of death somewhat greater than that incurred by a patient anesthetized with chloroform.

Effect of Dosage on Toxicity.—Plummer and Wheeler (1944) compared a group of 705 hospitalized patients given 6 gm. of sulfadiazine daily with 115 hospitalized patients given only 3 gm. daily; in the former group there were reactions of one sort or another in 9.2 per cent of cases whereas in the latter group there occurred only one reaction, a moderately severe drug fever, giving a percentage of 0.87. The disparity in size of the two groups is obviously very great, but even so the difference between the two percent-

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group there occurred reactions in 2 per cent of the patients. Coburn (1944) found that only 0.5 per cent of evanescent rashes and 0.01 per cent of dangerous constititutional disturbances occurred during the administration of 15 grains (1 gm.) of sulfadiazine daily for three months to 30,000 men. *It is therefore obvious that,* except for the matter of sensitization to be discussed below, the higher the dosage the greater the likelihood of reactions. However, there is another matter to be taken into account and that is the total dosage of the drug and the length of time during which it is administered. In this latter connection, the extensive data of Plummer and Wheeler definitely did not suggest that the patient who has been receiving the drug for more than three *or four weeks is safe from toxicity* as has sometimes been stated; indeed they concluded that in an individual case the longer the drug is continued the

greater is the chance of reaction in that case. However, the study of Kent and Diefendorf (1945) did not bear out the findings of Plummer and Wheeler, for in their 472 patients who received a course of sulfathiazole they found that if the patient had had no reaction after nine days of therapy his chances of developing one subsequently on the same administration diminished rapidly.

Effect of Route of Administration on Toxicity.—Of the 244 patients of Plummer and Wheeler (1944) who were given one or more intravenous injections of sulfadiazine, 12.3 per cent had some form of reaction as compared with 8.9 per cent of reactions in 912 patients treated orally with 6 gm. daily. The difference in the number of renal reactions in the two groups was more striking; in those given intravenous injections renal reactions occurred in 7.4 per cent, whereas in those treated orally such reactions occurred in only 4.5 per cent. There were two cases of mild and transitory jaundice with possible toxic [illegible]

[illegible]

knowledge that one is probably considerably increasing the likelihood of the occurrence of serious reactions.

Sensitization Through Local Application.—The local cutaneous application of sulfonamides, particularly sulfathiazole, gives rise in a not inconsiderable proportion of cases when administration is continued for more than a week to a contact type of dermatitis, with or without a disseminate eruption, or a local or generalized exacerbation of the skin disease for which the drug is being used. In some of these cases the local sensitization thus induced persists so that when the drug is taken internally at a later time there will be a return of the local signs of sensitization. *I have not seen any record of the occurrence* of visceral lesions as a result of this cutaneous sensitization, but that is no reason to minimize the seriousness of this occurrence since the skin reactions as a result of sensitization may be very severe indeed and force the discontinuance of sulfonamide therapy when it is direly needed for the treatment of a serious systemic infection. Furthermore, some of these skin reactions have themselves resulted fatally. The studies of Shaffer *et al.* (1943) and others showed that in some instances the sensitizing application of the drug may not produce local dermatitis and can only be shown retrospectively to have sensitized the patient when he is seen to respond very quickly and in a violent fashion to subsequent administration either locally or orally.

Sensitization Through Systemic Administration.—When an individual has received a sulfonamide for a week or more by mouth or parenterally and has developed a reaction of some sort, he is extremely likely to develop the same sort of reaction, but much more quickly and more violently, upon readministration of the drug after a lapse of time. In this connection witness the experience of Lee (1944), who recorded the administration for prophylactic purposes of a single 2 gm. dose of sulfadiazine to 25,000 Army personnel; there were only 128 reported reactions of any sort and only nine of these were considered to be "serious" but the important point is that seven of the nine occurred in patients who had previously experienced sulfonamide reactions. It is, however, not clearly established that a first course in which the patient develops no reaction may nevertheless sensitize him so that he will develop reactions upon subsequent administration. Indeed, the report of Siegel (1944) probably indicated with fair certainty that *short courses* of sulfadiazine may be frequently

doses. The maintenance dosage of sulfamerazine was from ½ to ¾ grain (30 to 45 mg.) per pound per day. It was noted in this study that the sulfonamides may produce or aggravate gastro-intestinal and neurologic disturbances in [illegible]

uncommon in the children and when present were usually associated with evidences of a general reaction such as fever and rash.

Occurrence of Reactions on Prophylactic Dosage.—Coburn (1944) reported that in the group of 30,000 Navy personnel to whom 15 grains (1 gm.) of sulfadiazine were administered daily during three months, evanescent rashes occurred in 0.5 per cent of the individuals and dangerous constitutional disturbances in only 0 01 per cent. There was only one death in the series, that of a man to whom therapeutic doses of sulfonamides were given while he had a sulfonamide rash and bronchitis induced by the prophylactic employment of the drug.

Lethality of the Toxic Reactions.—Plummer and Wheeler (1944) reported that at the New York Hospital only one death had occurred in 2853 patients given sulfadiazine in full therapeutic dosage. This is certainly a low rate, though there are other drugs ordinarily looked upon as rather toxic that have [illegible]

zine to a hospitalized patient under ideal circumstances he is nevertheless subjecting him to a risk of death somewhat greater than that incurred by a patient anesthetized with chloroform.

[illegible]

reactions of one sort or another in 9 2 per cent of cases whereas in the latter group there occurred only one reaction, a moderately severe drug fever, giving a percentage of 0.87. The disparity in size of the two groups [illegible]

group there occurred reactions in 2 per cent of the patients. [illegible] 0.5 per cent of evanescent rashes and 0.01 per cent of danger- [illegible]

is another matter to be taken into account and that is the [illegible] drug and the length of time during which it is administered. In this latter connection, the extensive data of Plummer and Wheeler *definitely* did not suggest that the patient who has been receiving the drug for more than three or four weeks is safe from toxicity as has sometimes been stated; indeed they concluded that in an *individual case* the longer the drug is continued the

[illegible]

zation to procaine also, a chemically related compound. Plummer and Wheeler's (1944) series of cases included only a few instances in which sulfadiazine was well tolerated by patients who had previously manifested toxic effects to sulfathiazole, but there were many examples of a similar type when sulfadiazine replaced sulfanilamide or sulfapyridine. The reverse of this, *i.e*, tolerance to the other sulfonamides after intolerance to sulfadiazine, occurred very infrequently. As a result of their very careful study of the matter, Plummer and Wheeler stated that no definite rules can be made for subsequent sulfonamide treatment in patients who have exhibited evidences of intolerance, except for the one rule that one must always be doubly cautious in such cases. They said that they had treated with great caution but successfully patients with past records of granulocytopenia, rashes and fever following the sulfonamides, and in most instances without repetition of the previous reactions; but they considered this practice to be a dangerous one that is to be avoided except in instances in which the necessity for reemployment of a sulfonamide is very urgent.

Desensitization to the Sulfonamides.—Tate and Klorfajn (1944) found that the usual method of beginning with very small doses and increasing in the attempt to desensitize as in any other allergic state was ineffective, for as small a dose as 1/250 of a grain (0.25 mg) given by mouth induced reappearance of the eruption. However, they did find that they could desensitize some of their worst cases by continuing sulfonamide administration in spite of further reactions in the skin, though the results were certainly severe and distressing for the patients O'Donovan and Klorfajn (1947) subsequently reported [illegible]
to [illegible]
0.1[illegible]
the allergic symptoms had disappeared and for ten days thereafter. This patient also was [illegible]

[illegible]

the employment of a sensitizing agent in the presence of a severe sensitization reaction only in cases of extreme emergency.

The Employment of Sulfonamide Mixtures.—Lehr (1945) introduced a new principle into sulfonamide therapy when he initiated the use of sulfonamide mixtures, reasoning that if not merely one but a mixture of several equivalent sulfonamides were employed, each contributing its fraction toward the maintenance of the total sulfonamide level, the risk of renal damage would be lessened since each of the drugs would be present in the mixture in a considerably lower individual concentration than would be necessary if it were used alone. Lehr *et al.* (1946) employed a mixture of sulfadiazine and sulfathiazole in equal parts in the treatment of 200 children with acute bacterial infections with results that were uniformly satisfactory, clinical toxicity was said to have been remarkably low, renal irritation did not occur, and crystalluria was infrequent despite the intentional omission of adjuvant alkali therapy The expectation of a possible increase in allergic reactions incident upon the simultaneous employment of two sulfonamides was not fulfilled, for the two cases exhibiting

repeated without fear of the establishment of sensitization; *i.e.*, if one does not administer the drug long enough in any course to sensitize the patient there is apparently little to fear. The number of Siegel's children treated twice for recurring acute infections of the upper respiratory tract was thirty-three; three times, twenty-three; four times, seventeen; five times, nine; six times, seven; seven to sixteen times, ten, treatment had to be interrupted in only three of the children because of an obvious intolerance to the drug, but the average duration of therapy in these cases was only four days.

employing intradermal injections of serum from patients receiving sulfonamides. Fink and Smith concluded, from their large-scale study in children, that if a complete history fails to disclose an earlier febrile reaction, a child

patient 0.5 gm. of sulfapyridine given twelve months after the original sensitization caused edema of the larynx; I have heard it stated that sensitization has been shown to persist for as long as three years but am unable to cite the records. It is probable, however, that most cases taper off in degree, for in a case of Dostrovski and Sagher (1944) the intensity of the fixed erythema

resulted only in a diminution of the vital respiratory capacity.

decidedly less effective in chronic eczematous processes; (b) and since the prolonged use of the agent is extremely likely to be productive of reactions; therefore (c) such therapy should not be prolonged for periods of more than five days. One could doubtless set up with equal justification this five-day rule with regard to the local use of the sulfonamides on mucous membranes and their prophylactic employment in acute respiratory infections. In more serious infections in which relatively prolonged administration is necessary it has simply to be expected that sensitizations will occur and that they can be minimized only by reducing the period of sulfonamide administration as sharply as is possible under the circumstances.

How May One Administer Sulfonamide to a Sensitized Individual?—Dowling *et al.* (1946) concluded that if a patient who has previously experienced a reaction must again be given a sulfonamide, he should receive a different drug from the one used in the first course, for they found that of seventy-eight patients receiving a second course of the same drug after showing a febrile, dermatologic or conjunctival reaction to the first course, 69 per cent developed toxic manifestations, while only 17 per cent experienced a toxic reaction

ter very intensively in forty sensitized patients.

is desirable to continue sulfonamide administration, occasional transfusions should be given. In the acute cases, however, there is definite indication to discontinue the use of the drug at once and to be sure that the urine remains alkaline in order to prevent deposition of the obstructing pigments in the renal tubules. *If it is necessary to continue the administration of the sulfonamides in the presence of an acute hemolytic anemia, then heroic use of blood transfusions must be made in the attempt to replace blood as rapidly as it is*

reaction and that therefore as few transfusions as possible should be given.

During the course of treatment with apparently any of the principal sulfonamides an *acute leukopenia* with granulocytopenia may occur, particularly in children and usually during the first ten days of therapy. In many clinics the

accompanied by angina are of much rarer occurrence; they have, however, been reported in association with the employment of all of the principal members of this series. This is a relatively late reaction, Kracke (1944) said that the drug has usually been given from one to three weeks before agranulocytosis develops. Nowadays, the prognosis is good if the nature of the reaction is recognized at its inception, administration of the drug is stopped at once, and penic-

reaction; i e, there may be a marked leukocytosis, the total number of leukocytes reaching 50,000 or more per cubic millimeter, the granulocytes sometimes also showing a marked degree of immaturity.

fanilamide, in far fewer treated with sulfapyridine, and very uncommonly in patients treated with sulfathiazole, sulfadiazine or any of the newer compounds. Most patients do not develop this sign until after considerable of the

...s unsettled, but Kracke

... stains the blood cells

...f methemoglobin. The

condition is considered to have little significance, but Wendel (1939) said that

allergic reactions represented an incidence of only 1 per cent. Flippin *et al.* (1946) have also found that a mixture in equal parts of sulfadiazine and sulfamerazine led to a markedly decreased incidence of crystalluria compared with that observed when either compound was administered singly. Frisk *et al.* (1947) reported upon the successful employment of a mixture of sulfathiazole, sulfadiazine and sulfamerazine in the proportions of 37 per cent, 37 per cent, and 26 per cent; a daily 90 grain (6 gm.) dose of this mixture thus provided only about one-third of the otherwise normal daily dose of each of the constituents. The sulfonamide blood levels attained and maintained were as good with the mixture as they would have been with sulfonamide alone in comparable total dosage; of the sulfonamide excreted in the urine about one-third was present in the acetylated form. It was said by Frisk *et al.* that they and others known to them had used this sulfonamide mixture with therapeutic satisfaction and without any known instances of renal calculi in "many hundreds" of cases. This new departure in therapy will certainly be watched with interest.

tization above. The local treatment is of course that indicated by the nature of ... In Johnson's (1944) case of

anemia is extr

of the series,

slowly developing hemolytic anemia in the course of which the patient's hemoglobin level drops 20 per cent or more *in the first ten* days of treatment, and another, a fulminating and very serious affair, usually occurring in the first five days of treatment, in which the hemoglobin and erythrocytes of the

of not longer than thirty-six hours. Other findings in the

macrocytosis, reticulocytosis, leukocytosis, and increased icterus index, urobilin in the urine, and in some cases hemoglobinemia and hemoglobinuria

of hemolytic anemia are not considered alarming

drug is stopped and may be combated

65 gm.) of ferrous sulfate daily; where it

ium. It is difficult to determine the absolute incidence of reactions of this nature but it is very evident that they occur much less frequently with sulfadiazine than with the earlier members of the series. Neither Reynolds and Shaffer (1943), nor Price and Pedulla (1944), were able to observe statistically valid changes in their attempt to make objective functional studies of these matters, but it nevertheless seems to me the part of wisdom for the physician to caution his patient to stay at home and rest while taking these drugs and not to make any important decisions or sign any papers during that time. Peripheral neuritis, myelitis and fatal encephalopathy have been reported, but such reactions are of extremely rare occurrence. As a result of their experience in nine cases of neuritis occurring in 1936 patients given full therapeutic sul-

curative value.

Therapy of Renal Disturbances.—The sulfonamides are acetylated, probably principally in the liver, and the acetylated together with much of the remaining free form of the drugs is excreted in the urine. In the case of the newer agents developed since the introduction of sulfanilamide the acetylated forms are relatively insoluble in the urine and hence tend to appear there in cryst

cause

also

bules, renal pelves, ureters and bladder—to cause the obstructive type of anuria. With the exception of sulfanilamide, which has rarely caused any kidney disturbance, sulfadiazine is offending less in this respect than any of the other currently used sulfonamides, the reason being that if the urine is kept alkaline acetylsulfadiazine is the most soluble of any of the acetyl derivatives

acid urine, whereas acetylsulfadiazine is more than twenty-five times as solu-

the administration of sufficient in each case to maintain a urine definitely alkaline. Methods of accomplishing this are discussed in the article on Pneumonia. Of course there should be an adequate fluid intake (3000 to 4000 cc in adults) in order to maintain a urinary output of 1200 to 1500 cc per day, but the reader should bear in mind that the attempt to prevent renal reactions by giving a high fluid intake has definite limitations as compared with alkalinization, since increasing the fluid intake twofold can only double the amount of acetylsulfadiazine dissolved whereas raising the urine from acid to alkaline in reaction will increase the solubility more than twenty-five times.

Arnett (1942) described a very practical method of keeping in touch with the status of the patient with regard to renal reactions by having the last urine passed exhibited at all times in a prominent place near the patient, *i.e.*,

"ceiling" by about 5000 feet, though Peterson *et al* (1945), of the Canadian Army, concluded from the study of persons subjected to simulated altitude that sulfathiazole in full therapeutic dosage does not significantly alter the ability of normal individuals to withstand the effects of altitude and that the use of the drug does not seem to be contraindicated for wounded personnel who are to be transported below 10,000 feet or above 10,000 feet with supplementary oxygen.

Therapy of Hepatic Disturbances.—Hepatitis was rarely observed in the sulfanilamide days and it occurs even more rarely with the newer drugs; for example, an occurrence described as "jaundice—possibly hepatitis" occurred in only 0.14 per cent of the 1357 sulfadiazine-treated patients of Plummer and Wheeler (1944) Menten and Andersch (1943), who studied the matter of hepatic damage in children, considered that it would appear desirable to *determine the role of inadequate nutrition as a factor in the vulnerability* of the liver to sulfonamides before finally evaluating the deleterious effects of these drugs upon the organ. The symptoms of such damage, according to Spring and Bernstein (1940), are anorexia, epigastric distress, nausea and at times vomiting, pain and tenderness in the right upper quadrant of the abdomen, jaundice, enlarged tender liver except in mild cases, hyperbilirubinemia, urobilinuria, biluria, and decreased hepatic function. Long (1940) made the practical point that jaundice with pale conjunctivae probably indi- ... the conjunctivae

... t sequelae if the drug administration is stopped at once and fluids are pushed; of course liberal carbohydrate administration is also indicated. In cases that have come to autopsy, focal hepatic necrosis has been most frequently found, diffuse hepatic necrosis much more rarely; it should be noted, however, that Herbut and Scaricaciottoli (1945) reported two fatal cases of the latter sort caused by sulfadiazine. *Many men feel that jaundice in itself contraindicates* continuance of therapy with the sulfonamides, but the jaundice due to pneumonia was not so considered by Flippin *et al.* (1941) even before the days of sulfadiazine; ... treated with ... d a ... ds

... found that: (a) in patients with acute hepatitis associated with ... infections, the sulfonamide therapy was almost invariably associated with improvement in hepatic function that paralleled the improvement in the underlying infection, (b) in patients with chronic damage to the liver, hepatic dysfunction was not aggravated by administration of sulfathiazole or sulfadiazine and there was some improvement noted as a result of such therapy in ... (c) severe ... were ... mon after sulfathiazole as after sulfadiazine

Therapy of Neuropsychiatric Disturbances.—It is now well known that the sulfonamides sometimes cause headache, dizziness, visual disturbances, confusion, disorientation, and other behavior abnormalities, depression with lethargy and somnolence, or the opposite state of exaltation and even delir-

taking one or other of these drugs is nevertheless frequently nauseated and depressed and complains of headache or other symptoms Upon the other hand, the patient taking sulfadiazine usually makes very little complaint; nausea or loss of appetite is rare, his color is normal and he is not depressed There is very little to do for these minor reactions.

Sulfonamide Antidotes.—It does not seem to me that there are any. The assertion has been made that ascorbic acid is of value, but Dowrie and Abramson (1944), who administered large doses of this vitamin orally to twenty-five children, did not find that it had any detoxifying effect upon either sulfathiazole or sulfadiazine. Detoxication by liver extract has been reported in experimental animals but I have not seen any convincing evidence of its value in man.

Sulfonamides and Diet.—During the early days of therapy with the drugs of this group, when it was thought that cyanosis was of serious import, severe dietary restrictions were made in order to reduce the amount of sulfur absorption and thus perhaps also limit the production of sulfhemoglobinemia. Now such restrictions are definitely outmoded because cyanosis has been put in its

liquors as they greatly increase the tendency toward, and the degree of, the psychotic reactions to the sulfonamides

Sulfonamides and Other Drugs.—There exists indubitable evidence in animal experimentation of the summation effects of the sulfonamides and the sedatives and general anesthetics But I am unaware of any real substantiation of these findings in the human Adriani and St. Romain (1942), who reported some of the positive findings in the lower animals, were obliged to report negative findings in man, at least the anesthesias proceeded quite normally in a series of twenty-three patients given cyclopropane, twenty-five given ether and five given pentothal, all of the patients having received the usual premedication with morphine and scopolamine or atropine and some of them receiving in addition seconal, phenobarbital, or pentobarbital Experience in War II certainly amply showed that one does not need to fear the use of general

Finland *et al* (1943) showed that procaine (novocaine) in amounts ordinarily

each time the patient voids, the old sample is discarded and the new one substituted. "The nurse sees it," said Arnett, "the intern *sees it, and I see* it (or if I do not I ask the reason why)." If the urine contains many sulfonamide crystals when it is first passed it looks muddy, but the crystals soon settle

and the urine is kept alkaline and the fluid balance is maintained

ure including decapsulation with nephrostomy, was found at autopsy to have thrombosis of both renal arteries, a complication thought not to have been previously reported.

Finegold (1946) reported an unusual type of reaction consisting of anuria with findings indicative of angioneurotic edema of the ureters and bladder ... attack of asthma.

other types which there us organs involved in a widespread focal necrotic type of reaction, now believed to occur

gardless of what other changes were present; in some this process was advanced and there was necrosis of the tubular cells and intense inflammatory reaction outside the nephron in the surrounding tissues In one case advanced changes in the glomeruli were observed. Of course there is nothing to say regarding therapy in these cases except to note that in the one patient of Murphy *et al.* who recovered decapsulation of the kidney had been performed

Therapy of Cardiovascular Reactions.—Sometimes at autopsy it has been observed that the myocardium has shared in the widespread focal necrotic

cardiogram Comparable changes in the smaller blood vessels may, however,

analgesic agents do not control this pain; however, ... (1943) reported the case of a patient, being treated for colitis, in whom both

infecting organisms leaves the tissues of the body to dispose of the resulting débris to an extent not before known. They said that this altered reaction to injury of the body tissue by infection often roentgenologically simulates neoplasm and may be easily confused with syphilis and other conditions, thus posing a considerable problem for the roentgenologist

However, certainly by far the most frequently occurring reaction to penicillin given parenterally is urticaria. These urticarias occurring in association with penicillin therapy are very bizarre, they may occur at the beginning, several days after the institution, or several days—perhaps even as long as a month—after the termination of therapy.

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Pillsbury *et al.* (1947), on the basis of a considerable experience with urticarial and other allergic reactions to penicillin, recommended a scheme of management of such reactions as follows. (a) Stop the administration of penicillin immediately, except possibly in occasional instances in which there is a critical need on the part of the patient for the drug (b) Administer benadryl or pyribenzamine in a dosage of 50 to 100 mg three times daily by mouth to adult patients, and expect that the effectiveness or lack of same will ordinarily become apparent within twelve hours, though it may be necessary in some instances to administer the antihistamine compound as often as every four hours round the clock (c) If the reaction to penicillin is severe, or if it is considered necessary to continue its administration without interruption despite [illegible]

Upon the subsidence of the urticaria and accompanying symptoms a test dose of 1000 units of another manufacturer's penicillin may be administered intramuscularly, provided that facilities for the administration of epinephrine or of benadryl intravenously are at hand; it is recommended that the administration of an antihistamine drug by mouth be continued during this period (e) If no reaction to the test dose occurs within six hours another dose of 10,000 to 20,000 units may be given, and if this does not cause a reaction within four hours the administration of penicillin may be resumed in full therapeutic doses, though with continued administration of the antihistamine compound. (f) Thereafter the attempt should be made to discontinue the antihistamine compound gradually, this may be successfully done in some instances while continuing the administration of penicillin (g) It is considered advisable during the period of the trial administration of penicillin not to use it in peanut oil and beeswax but rather in a form that will be rapidly excreted should a reaction occur. (h) If the immediate attempt to readminister penicillin is not successful it is advised that one wait a month or more and then make another very cautious attempt if it is still considered necessary to give the drug

PENICILLIN REACTIONS

Apparently penicillin has a directly irritating effect when introduced intrathecally, the irritant residing in the penicillin itself and not in the impurities; this matter is fully discussed in Sepsis. The agent also induces the Herxheimer reaction, a subject dealt with in the article on Syphilis The intramuscular injection of amorphous penicillin sometimes causes brief sharp pain, but this reaction is seen much less frequently than formerly and practically never occurs when crystalline penicillin G is injected. The important subject of venous irritation and thrombosis when penicillin is given by continuous intravenous drip is discussed in Endocarditis.

The skin reactions resulting from the systemic administration of penicillin include urticaria, either generalized or localized, morbilliform rashes, vesicular eruptions, ecchymoses, purpuric eruptions, and eruptions typical of toxic erythema multiforme as well as those characteristic of erythema nodosum. There have been a number of reports of the aggravation of preexisting skin diseases of wide variety, and it seems that penicillin not infrequently aggravates fungus infections and that fungus infections may cause increased reactivity to penicillin. There is good evidence that reactions do not follow the ... any more frequently than they do the

es. That the

or the bees-

ized by the

tive.

Joint involvement and reactions simulating serum sickness have been reported, as have also gastro-intestinal disturbances. Barksdale (1946) said that at the Naval Hospital at Bethesda several cases of neuritis due to penicillin have been seen and that complaints of pain in the peroneal nerve have been frequent Five cases of complete foot drop were observed, two of the cases requiring five months to clear up

Many patients object to the taste and smell of the aerosolized amorphous penicillin and find it irritant to the tongue or the oropharynx, these complaints being often minimized by a change to other lots of the drug. A few patients develop black and sore tongues or stomatitis Segal and Ryder (1947) recorded a few cases of edema of the lips or the mucosa of the mouth When crystalline penicillin G, which is virtually free of all impurities and tissue irritants, is used in aerosol therapy it apparently does not cause any blackening of the teeth, the gums or the tongue, and probably does not cause as much upper respiratory ... salts

pointed out that the introduc-

ulfonamides and more particu-

nost significant and previously

killing or attenuating of the

infecting organisms leaves the tissues of the body to [illegible]

several days after the institution, or several days—perhaps [illegible] month—after the termination of therapy.

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Note. The various diseases, important complications and symptom complexes are indicated by **bold-face type.**

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